Evaluating causal effects on time-to-event outcomes in an RCT in Oncology with treatment discontinuation due to adverse events

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Abstract

In clinical trials, patients sometimes discontinue study treatments prematurely due to reasons such as adverse events. Since treatment discontinuation occurs after the randomisation as an intercurrent event, it makes causal inference more challenging. The Intention-To-Treat (ITT) analysis provides valid causal estimates of the effect of treatment assignment; still, it does not take into account whether or not patients had to discontinue the treatment prematurely. We propose to deal with the problem of treatment discontinuation using principal stratification, which is recognised in the ICH E9(R1) addendum as a strategy for handling intercurrent events. Under this approach, we can decompose the overall ITT effect into principal causal effects for groups of patients defined by their potential discontinuation behaviour in continuous time. In this framework, we must consider that discontinuation happening in continuous time generates an infinite number of principal strata; furthermore, discontinuation time is not defined for patients who would never discontinue. An additional complication is that discontinuation time and time-to-event outcomes, which are often the main endpoints in clinical trials, are subject to administrative censoring. We employ a flexible model-based Bayesian approach to deal with such complications. We apply the Bayesian principal stratification framework to analyse synthetic data based on a recent clinical trial in Oncology, aiming to assess the causal effects of a new

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investigational drug combined with standard of care versus standard of care alone on progressionfree survival. We simulate data under different assumptions that reflect real situations where patients' behaviour depends on critical baseline covariates. Finally, we highlight how such an approach makes it straightforward to characterise patients' discontinuation behaviour with respect to the available covariates with the help of a simulation study.

Keywords: Causal inference; Censoring; MCMC; Potential outcomes; Principal stratification.

1 Introduction

Randomised controlled trials (RCTs) are the gold standard for assessing causal effects in medical studies. RCTs, however, may suffer from complications that are not under experimental control: phenomena such as noncompliance, treatment switching or treatment discontinuation are all events that break initial randomisation since they occur after it, and they can either preclude observation of the outcome of interest or affect its interpretation. Recently, an addendum to the E9 guide-line on "Statistical principles in clinical trials" has been released by the International Council of Harmonization (ICH), where these types of events are referred to as *intercurrent events* [ICH, 2020].

The case study that motivated this work consists of a clinical trial in which premature treatment discontinuation can occur, and questions were raised to understand better the effect of a partial receipt of the treatment in the subgroup of patients who discontinued. In particular, we deal with an RCT in Oncology aimed to assess the causal effects of a new investigational drug combined with standard of care versus standard of care only on progression-free survival, i.e., the time from randomisation until disease progression or death. In the case of adverse events (AEs), e.g., side effects, patients enrolled in the investigational treatment arm can prematurely discontinue the treatment. In such a context, and also in line with the tripartite estimand strategy [Akacha et al., 2017], relevant questions to patients, physicians, pharmaceutical companies, and regulatory agencies concern i) the treatment effect for patients who adhere to the treatment for its intended duration, ii) the proportion of those who discontinue the investigational treatment prematurely, and iii) the effect for patients who discontinue the treatment prematurely. The latter patients could still derive a benefit from taking the treatment initially. For example, Schadendorf et al. [2017] investigate such questions from a clinical perspective for a new treatment in Oncology.

To face the issues that may concern different stakeholders, we propose to deal with the problem of estimating treatment effect in the presence of premature treatment discontinuation using the principal stratum strategy, which is introduced by the ICH E9 Addendum (ICH, 2020) to provide valid causal estimands in the presence of intercurrent events. The principal stratum strategy refers to the principal stratification framework by Frangakis and Rubin [2002]. Principal stratification (PS) focuses on causal effects for patients belonging to latent subpopulations, namely the "principal strata", defined by the post-randomisation variable of interest; in this work, by the premature discontinuation behaviour.

Treatment discontinuation can be viewed as a form of partial noncompliance; namely, patients take only part of the assigned dose. If we consider the patients who can tolerate the treatment for its intended duration as *compliers*, it is natural to resort to PS. Indeed, noncompliance is a natural application of PS since Frangakis and Rubin [2002], and even before their formalisation; see Angrist et al. [1996] and Hirano et al. [2000]. Since then, key methodological contributions to the topic have been made during the last two decades; among many others, see Mealli et al. [2004], Mattei and Mealli [2007], Roy et al. [2008], Jin and Rubin [2008], Schwartz et al. [2011], Sheng et al. [2019], Jiang and Ding [2021], and Liu et al. [2023].

Recent reviews of the principal stratum strategy in the context of clinical trials in drug development have been given by Bornkamp et al. [2021] and Lipkovich et al. [2022]. Articles showing the potential of principal stratification often rely on dated case studies (see Jin and Rubin [2008], Schwartz et al. [2011], among others).

Yet, motivated by a recent RCT in Oncology, we can deal with and specify a problem-driven model that could address substantive research questions under different scenarios. In this article, we provide a method to answer questions raised during the last years by the pharmaceutical community [Akacha et al., 2017, Qu et al., 2020, 2021], specifically addressing the treatment discontinuation problem in continuous time. In terms of *efficacy*, we can provide well-defined estimands for measuring treatment effects for those who potentially adhere to the treatment for its intended duration and causal effects for those who potentially discontinue the treatment at a certain time. Our model can also estimate the percentage of patients that discontinue the treatment and, leveraging the available covariates, the probability that a specific patient will discontinue the treatment and after how long.

Previous works exploited the advantages of a Bayesian approach for inference in a PS framework when dealing with post-randomisation events occurring in clinical trials; see Magnusson et al. [2019], Ohnishi and Sabbaghi [2022] and Mattei et al. [2023a]. In this work, the Bayesian approach allows us to properly take into account that the discontinuation time is either not defined (for those who would never discontinue) or continuous; in the latter case, it generates a continuum of principal strata. Moreover, we consider that both survival time and discontinuation time are subject to censoring. Although it addresses a different problem, our model is indeed similar to that in Mattei et al. [2023a], under the common framework of the PS. However, our approach overcomes the limits of Mattei et al. [2023a], whose application cannot be targeted for current policy interests and cannot shed light on the role of the covariates in this framework.

The following Section introduces the case study that motivated this work. Section 3 presents our principal stratum strategy, recalling the potential outcomes approach and defining the principal strata and the respective principal causal estimands. Section 4 sets the model and the inference in a fully Bayesian framework. Section 5 shows how we perform the analyses under different scenarios via a simulation study and the results we obtain in each scenario using a single data set. The simulation study highlights the role of covariates in improving the precision of causal effects estimates; Section 6 shows that the covariates can also be used to inform about the risk of AEs and characterise the PS. The discussion follows. Some details of this work are discussed in the Supplementary Material available online.

2 The case study

The case study that motivated this work deals with a recent RCT in Oncology, aiming to assess the causal effects of a new investigational drug combined with the standard of care (SOC) versus SOC on progression-free survival, i.e., the time from randomisation until a primary event that can be either disease progression or death. The study duration from the first randomised patient to the analysis cutoff date is approximately c = 33 months. All patients were enrolled during the first 23 months; thus, each patient can have a different follow-up period (or time to censoring)



Figure 1: Illustration of patients' journeys in the specific trial. Patients 1 to 4 are assigned to the investigational treatment plus SOC, whereas Patients 5 and 6 are assigned to the SOC only. During the follow-up period, in the treatment arm: Patient 1 remains on treatment for its intended duration; Patient 2 discontinues the treatment due to AE and continues with SOC; Patient 3 discontinues due to AE and then experiences a primary event; Patient 4 experiences the primary event without discontinuing the treatment. On the control arm: Patient 5 experiences the primary event, while Patient 6 does not.

 $C_i \in [10, 33]$. Let Z_i denote the treatment assigned to the i^{th} patient, and let z_i denote a realisation of Z_i ; z_i can be either 1, if i is assigned to the new investigational treatment - in addition to SOC (investigational treatment), or 0 if i is assigned SOC only (control treatment). Among n = 335patients, $n_1 = 181$ were assigned to the new investigational treatment, and $n_0 = 154$ were assigned to SOC. When patients in the new treatment arm incurred AEs, they were allowed to discontinue the new investigational treatment but continued on SOC. Figure 1 show the possible patients' journeys. We denote with $\tilde{D}_i^{\text{obs}} = \min(D_i^{\text{obs}}, C_i)$ and $\tilde{Y}_i^{\text{obs}} = \min(Y_i^{\text{obs}}, C_i)$ the censored discontinuation time and the time to primary event, respectively. The baseline information available consists of the following covariates:

- X_1 : continuous variable. The higher the value of X_1 , the higher risk of progression;
- X_2 : binary indicator for metastatic status. $X_2 = 1$ denotes higher progression risk;
- X_3 : binary indicator for disease burden. As for X_2 , $X_3 = 1$ denotes higher progression risk.

For confidentiality reasons, here we use summary statistics based on synthetic data generated using

Variable	Mean(proportion)	\mathbf{SD}	Min	Q1	Median	$\mathbf{Q3}$	Max
$\overline{Z_i = 1}$	54.00% (181/335)						
$\mathbb{I}(D_i^{\text{obs}} < C_i)$	16.57%(30/181)						
$\tilde{D}_i^{\mathrm{obs}}$	3.72	5.04	0.26	1.07	1.41	4.09	24.11
$\mathbb{I}(Y_i^{\text{obs}} < C_i)$	66.00% (221/335)						
$ ilde{Y}^{ m obs}$	6.60	5.95	0.10	1.87	3.81	9.17	27.63
Continuous covariates							
X_1	63.27	10.50	25.00	57.00	63.00	71.00	92.00
Categorical covariates							
X_2	43.90% (147/335)						
X_3	23.90%~(80/335)						

Table 1: Summary statistics of synthetic data. Here n = 335, $n_1 = 181$, and n = 154.

real case data. The statistics are summarized in Table 1. This gives us the opportunity to simulate individual data with different hypothetical assumptions of treatment effects to test our model performance; see Section 5.

3 Methods. A principal stratum strategy

Consider the randomized controlled clinical trial described in the previous Section. Applying the widespread Intention-To-Treat (ITT) principle would provide valid causal estimates of the treatment assignment, neglecting the premature treatment discontinuation; as the name suggests, it is a treatment policy estimand and does not always inform on treatment efficacy.

We apply the principal stratification framework [Frangakis and Rubin, 2002] and define causal estimand on the treatment effect that can capture the effect heterogeneity with respect to the discontinuation time.

3.1 Potential outcomes approach

Principal stratification heavily relies on the potential outcomes (or "Rubin causal") model [Rubin, 1974]. Under the Stable Unit Treatment Value Assumption (SUTVA; Rubin [1980]), let $Y_i(z_i)$ be the potential progression-free survival time for the i^{th} unit under treatment assignment z_i . When the patients incur AEs due to the investigational treatment, they can discontinue the new treatment so that they are treated with SOC only. On the contrary, patients under control treatment cannot receive the investigational treatment. Let $D_i(z_i)$ be the potential time to discontinuation of unit *i* under treatment assignment $Z_i = z_i$.

Since the discontinuation of the new treatment is possible under investigational treatment only, the discontinuation time is not defined under control. This scenario is similar to a randomized study with one-sided partial compliance, although the time-to-event nature of the discontinuation behaviour makes it particularly challenging. Following Mattei et al. [2023a], we formally set $D_i(0) = \overline{\mathbb{D}} \forall i$, meaning that $D_i(0)$ takes on a non-real value. Yet, patients are allowed to discontinue the investigational treatment as far as they do not experience the primary event. We say that $D_i(1)$ is censored by death or progression; indeed, $D_i(1) < Y_i(1)$. Therefore, on the one hand, for those who potentially discontinue, $D_i(1)$ is defined in \mathbb{R}^+ . On the other hand, for the units who experience the event without discontinuing (either before or after the follow-up period), the time to discontinuation is not defined, i.e., $D_i(1) = \overline{\mathbb{D}}$. The study duration is limited to c months, and each patient can enter the study at a different time, implying different censoring times $C_i(z_i) \leq c$ under treatment assignment $Z_i = z_i$. We assume that $C_i(1) = C_i(0) = C_i \forall i$ and that the censoring mechanism is ignorable given the covariates X_i , i.e.,

$$P(C_i|D_i(1), Y_i(1), Y_i(0), \boldsymbol{X}_i) = P(C_i) .$$
(1)

3.2 Principal strata and causal estimands

According to their discontinuation behaviour, the units are classified into different (latent) subpopulations, or *principal strata*. Since $D_i(0) = \overline{\mathbb{D}}$, $\forall i$, treatment discontinuation is one-sided; thus, the strata are defined exclusively with respect to the discontinuation behaviour under new treatment, $D_i(1)$. Since $D_i(1)$ is either not defined or continuous, units can be either patients that would not discontinue if assigned to the investigational treatment, i.e., those *i* such that $D_i(1) = \overline{\mathbb{D}}$, or patients that would discontinue at a time $d \in \mathbb{R}^+$. We refer to the former patients as "Never Discontinuing" (ND patients) and to the latter as "Discontinuing" (D patients) throughout the paper. Given that the discontinuation variable is continuous, the group of patients who would discontinue at some point in time is the union of infinite basic principal strata D.

Under such a principal stratification approach, we can decompose the ITT effect defining principal

causal estimands, namely causal estimands for each latent subpopulation.

In the case of *average* causal effects, the ITT effect would be a weighted average of *principal* average causal effects, i.e., average causal effects conditional for the discontinuation behaviour:

$$ITT = \pi_{\rm ND} A C E_{\rm ND} + (1 - \pi_{\rm ND}) A C E_{\rm D} , \qquad (2)$$

where $\pi_{\rm ND}$ is the proportion of ND patients, and $ACE_{\rm ND}$ and $ACE_{\rm D}$ are the average causal effects for ND and D patients, respectively.

Characterising the ITT effect heterogeneity with respect to the discontinuation time is challenging because the discontinuation can be *non-ignorable*, i.e., the discontinuation status is not necessarily independent of the potential outcomes even conditional on covariates: $Y_i(1), Y_i(0) \not\perp D_i(1) | \mathbf{X}_i$.

We may define *population* principal average causal effects as follows.

• for ND patients:

$$ACE_{\rm ND} = \int_{\mathcal{X}} \left\{ \mathbb{E}[Y(1) \mid D(1) = \bar{\mathbb{D}}, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y(0) \mid D(1) = \bar{\mathbb{D}}, \boldsymbol{X} = \boldsymbol{x}] \right\} \hat{f}(\boldsymbol{x}) d\boldsymbol{x} , \quad (3)$$

• for D patients:

$$ACE_{\rm D} = \int_{\mathbb{R}^+} ACE_{\rm D}(D(1) = d) f_D(d) \, \mathrm{d}d \,, \tag{4}$$

where $f_D(d)$ is the density of D(1), and

$$ACE_{\mathrm{D}}(d) = \int_{\mathcal{X}} \left\{ \mathbb{E}[Y(1) \mid D(1) = d, \boldsymbol{X} = \boldsymbol{x}] - \mathbb{E}[Y(0) \mid D(1) = d, \boldsymbol{X} = \boldsymbol{x}] \right\} \hat{f}(\boldsymbol{x}) d\boldsymbol{x}$$
(5)

for all $d \in \mathbb{R}^+$. In Equations (3)-(5), $\hat{f}(\boldsymbol{x})$ is the empirical multivariate distribution of \boldsymbol{X} [in fact, those in (3) and (5) can be more properly called *mixed* effects; see Li et al., 2023].

Finally, we define the distributional causal effects of the treatment (or principal survival difference) at time y, in a similar fashion to Mattei et al. [2023a]. The distributional causal effect at y for the set of ND patients is:

$$DCE_{\rm ND}(y) = \int_{\mathcal{X}} \{ P\{Y(1) > y \mid D(1) = \bar{\mathbb{D}}, \boldsymbol{X} = \boldsymbol{x} \}$$

$$- P\{Y(0) > y \mid D(1) = \bar{\mathbb{D}}, \boldsymbol{X} = \boldsymbol{x} \} \} \hat{f}(\boldsymbol{x}) d\boldsymbol{x}, \quad y \in \mathbb{R}_{+},$$

$$(6)$$

whereas the distributional causal effects of the treatment at time y for those who would discontinue at time d had they survived until time d if assigned to treatment is:

$$DCE_{D}(y \mid d) = \int_{\mathcal{X}} \{ P\{Y(1) > y \mid D(1) = d, \mathbf{X} = \mathbf{x} \}$$

$$- P\{Y(0) > y \mid D(1) = d, \mathbf{X} = \mathbf{x} \} \} \hat{f}(\mathbf{x}) d\mathbf{x}, \quad y, d \in \mathbb{R}_{+}.$$
(7)

3.3 Potential outcomes and observed data

Considering the censoring, once the treatment has been assigned, the observed progression-free survival and the observed discontinuation time for each unit i are $\tilde{Y}_i^{obs} = \min(Y_i^{obs}, C_i)$, and

$$\tilde{D}_{i}^{obs} = \begin{cases} \min \left\{ D_{i}^{obs}, C_{i} \right\} & \forall i : Z_{i} = 1, D_{i}^{obs} \in \mathbb{R}^{+} \\ C_{i} & \forall i : D_{i}^{obs} = \bar{\mathbb{D}} \end{cases}$$

$$\tag{8}$$

where

$$Y_i^{obs} = Z_i Y_i(1) + (1 - Z_i) Y_i(0), \quad \text{and} \quad D_i^{obs} = Z_i D_i(1) + (1 - Z_i) \bar{\mathbb{D}} .$$
(9)

According to their behaviour, it is possible to categorise different patients' profiles. Table 2 summarises the observed profile. Under treatment, among those who have experienced the primary event during the follow-up ($\tilde{Y}_i^{\text{obs}} = Y_i^{\text{obs}}$), there may be D patients, namely, those who had discontinued the treatment ($\tilde{D}_i^{\text{obs}} = D_i^{\text{obs}}$), and patients who had not ($\tilde{D}_i^{\text{obs}} = C_i$) and hence are ND patients undoubtedly. Among those who have not experienced the primary event during the followup ($\tilde{Y}_i^{\text{obs}} = C_i$), there may be patients who have discontinued the treatment (D) and patients who have not; the latter set is a mixture of ND and D at time $d > C_i$. Under control, we cannot observe the patients' behaviour under treatment; their profiles are thus infinite mixtures of units who would have discontinued at time $d, 0 < d < Y_i^{\text{obs}}$, and units who would have never discontinued if assigned

Z_i	\tilde{Y}_i^{obs}	$\tilde{D}_i^{\mathrm{obs}}$	Principal stratum label
1	$Y_i^{\rm obs}$	$D_i^{\rm obs}$	D
1	$Y_i^{\rm obs}$	C_i	ND
1	C_i	D_i^{obs}	D
1	C_i	C_i	D or ND
0	Y_i^{obs}	C_i	D or ND
0	C_i	C_i	D or ND

Table 2: Observed profiles according to the observed discontinuation behaviour.

to the investigational treatment.

4 Bayesian inference

Even under initial randomisation, i.e., $Y_i(1), Y_i(0), D_i(1) \perp Z_i$, which holds by design in an RCT, and the assumption of completely ignorable censoring (see Equation (1)), the causal estimands described in Section 3.2 are not fully nonparametrically identifiable from the observed data. Aiming at estimating the treatment causal effect for each stratum, we adopt a Bayesian approach, which does not require full identification [Lindley, 1972]. Within the framework of the Bayesian causal inference [Li et al., 2023], in this Section, we provide a general setting to model the intermediate variable and the potential outcomes given the intermediate variable.

4.1 Model setting

To each unit *i* we associate the following quantities: $Z_i, C_i, Y_i(1), Y_i(0), D_i(1), X_i$. We observe $Z_i, C_i, \tilde{Y}_i^{obs}, \tilde{D}_i^{obs}, X_i$ for each *i*. Therefore, $Y_i(Z_i)$ is only observed for units who experienced the event under treatment Z_i ; $D_i(1)$ is only observed for some *i*, namely the D patients assigned to treatment whose discontinuation time is not censored. However, $Y_i(1-Z_i)$ is missing for all *i*. Note that, under a Bayesian approach, Y_i^{obs} is a realisation of $Y_i(1)$ for the units assigned to treatment and of $Y_i(0)$ for those assigned to the control. Similarly, D_i^{obs} is a realisation of $D_i(1)$ for the units assigned to control.

The joint distribution of the quantities described above is $\pi(Z_i, C_i, Y_i(1), Y_i(0), D_i(1), X_i | \theta)$, with θ being the parameter (vector) that governs the joint distribution. Such distribution can be factorised as follows:

$$\pi(Z_{i}, C_{i}, Y_{i}(1), Y_{i}(0), D_{i}(1), \mathbf{X}_{i} \mid \boldsymbol{\theta}) =$$

$$= \pi(Z_{i} \mid C_{i}, Y_{i}(1), Y_{i}(0), D_{i}(1), \mathbf{X}_{i}; \boldsymbol{\theta}) \pi(C_{i} \mid Y_{i}(1), Y_{i}(0), D_{i}(1), \mathbf{X}_{i}; \boldsymbol{\theta})$$

$$\times \pi(Y_{i}(1) \mid Y_{i}(0), D_{i}(1), \mathbf{X}_{i}; \boldsymbol{\theta}) \pi(Y_{i}(0) \mid D_{i}(1), \mathbf{X}_{i}; \boldsymbol{\theta}) \pi(D_{i}(1) \mid \mathbf{X}_{i}; \boldsymbol{\theta}) \pi(\mathbf{X}_{i} \mid \boldsymbol{\theta})$$
(10)

Under randomisation, assuming exchangeability and the ignorability of the censoring mechanism, we only need to model the potential outcomes and the potential discontinuation to make inferences on the causal estimands described in Section 3.2. We do not directly model the covariates' vector since we are interested in what we refer to as *mixed effects*, and thus we condition on the empirical distribution of the covariates $\hat{f}(\boldsymbol{x})$ [again, see Li et al., 2023]. No additional structural assumptions are made, such as *principal ignorability*, exclusion restriction [Mattei et al., 2023b].

Let us start defining a two-part model for the discontinuation variable; the first categorical part models the membership to the group of ND patients versus the group of D ones. We denote with

$$\mathbf{I}_{i}^{\mathrm{ND}} = \mathbb{I}_{\{D_{i}(1)=\mathbb{D}\}} = \mathbf{I}_{i}^{\mathrm{ND}}(\boldsymbol{\theta}^{\mathbb{\bar{D}}}, \boldsymbol{X}_{i}) , \qquad (11)$$

the discontinuation indicator taking value 1 when the unit *i* is ND; we let the probability of I_i^{ND} be function of the *K*-dimensional vector of covariates $\boldsymbol{X}_i = (X_{i,1}, \dots, X_{i,K})$ and of parameters $\boldsymbol{\theta}^{\mathbb{D}}$.

The second part of the model deals with the potential time-to-discontinuation $D_i(1)$, conditional on the discontinuation status and the covariates X_i . We assume

$$D_{i}(1)|\mathbf{I}_{i}^{\mathrm{ND}}, \mathbf{X}_{i} \begin{cases} = \bar{\mathbb{D}} & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{D}(\cdot; \boldsymbol{\theta}^{D}, \mathbf{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 , \end{cases}$$

$$(12)$$

i.e., the discontinuation time is not defined for the ND patients, while for D patients it follows a generic suitable distribution $\psi(\cdot; \theta^D, X_i)$ depending on some parameters θ^D and covariates X_i .

Then, we model the potential survival outcomes assuming that they are conditionally independent given the discontinuation status and time and given the covariates and the parameters' vector. Let the potential outcome under treatment conditionally be:

$$Y_{i}(1)|\mathbf{I}_{i}^{\mathrm{ND}}, D_{i}(1), \boldsymbol{X}_{i} \begin{cases} \sim \psi_{\bar{1}}(\cdot; \bar{\boldsymbol{\theta}}^{1}, \boldsymbol{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{1}(\cdot; \boldsymbol{\theta}^{1}, \boldsymbol{X}_{i}, D_{i}(1)) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 . \end{cases}$$

$$(13)$$

By the natural constraint, $Y_i(1) > D_i(1)$; thus, the conditional potential outcome under investigational treatment for D patients must be a truncated variable.

We assume the potential outcome under control $Y_i(0)$ to be independent of $Y_i(1)$ given $D_i(1)$ and the covariates but not independent of the discontinuation status;

$$Y_{i}(0)|\mathbf{I}_{i}^{\mathrm{ND}}, D_{i}(1), \boldsymbol{X}_{i} \begin{cases} \sim \psi_{\bar{0}}(\cdot; \bar{\boldsymbol{\theta}}^{0}, \boldsymbol{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{0}(\cdot; \boldsymbol{\theta}^{0}, \boldsymbol{X}_{i}, D_{i}(1)) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 . \end{cases}$$

$$(14)$$

Here, the potential outcome under control for D patients can also be a function of the discontinuation time.

We assume that the elements of the parameter vector $\boldsymbol{\theta} = (\boldsymbol{\theta}^{\mathbb{D}}, \boldsymbol{\theta}^{D}, \bar{\boldsymbol{\theta}}^{1}, \boldsymbol{\theta}^{1}, \bar{\boldsymbol{\theta}}^{0}, \boldsymbol{\theta}^{0})$ are a priori independent. Hence, we write the joint prior distribution of $\boldsymbol{\theta}$ as

$$\pi(\boldsymbol{\theta}) = \pi(\boldsymbol{\theta}^{\mathbb{D}})\pi(\boldsymbol{\theta}^{D})\pi(\bar{\boldsymbol{\theta}}^{1})\pi(\boldsymbol{\theta}^{1})\pi(\bar{\boldsymbol{\theta}}^{0})\pi(\boldsymbol{\theta}^{0}) .$$
(15)

4.2 Posterior computation

Our aim is to draw from the posterior distribution

$$\pi(\boldsymbol{\theta} \mid \boldsymbol{X}, \boldsymbol{Z}, \boldsymbol{C}, \tilde{\boldsymbol{D}}^{\text{obs}}, \tilde{\boldsymbol{Y}}^{\text{obs}}) \propto \mathcal{L}(\tilde{\boldsymbol{Y}}^{\text{obs}}, \tilde{\boldsymbol{D}}^{\text{obs}}; \boldsymbol{\theta}, \boldsymbol{X}, \boldsymbol{Z}, \boldsymbol{C}) \pi(\boldsymbol{\theta}) , \qquad (16)$$

where $\mathcal{L}(\tilde{Y}^{\text{obs}}, \tilde{D}^{\text{obs}}; \theta, X, Z, C)$ is the observed data likelihood. Given the presence of infinite mixtures in the likelihood function, following Mattei et al. [2023a], we rely on a data augmentation procedure and estimate the posterior via MCMC. Further details can be found in the Supplementary Material. Note that once we are able to draw from (16), we can estimate the posterior distribution of any causal estimand of interest beyond those introduced in Section 3.2.

5 Application and results

5.1 Synthetic data

In this article, we illustrate two scenarios of interest. The first scenario depicts a situation in which the principal causal effects are positive in all the latent strata, reflecting the efficacy of the treatment. The second scenario represents a more challenging case of a positive overall effect, i.e., ITT > 0, but the treatment assignment has no effect for D patients; $ACE_{\rm D} = 0$, $DCE_{\rm D} = 0$; in other words, we mimic a situation in which the treatment does not show efficacy due to discontinuation. The summary statistics of the data simulated under such scenarios are very close between them and similar to the summaries of the real data; Tables are shown in the Supplementary Material.

In both scenarios, we make some assumptions on discontinuation for synthetic data simulation.

- The higher the value of X_1 , the lower the probability of being a ND patient.
- Patients with X_2 , X_3 equal to 1 are more likely to be ND patients, i.e., patients who experience progression-free survival (PFS) without discontinuing.
- For D patients, those with higher risk are more likely to discontinue sooner.

5.1.1 Scenario I: $ACE_{ND} > 0$, $ACE_{D} > 0$, $DCE_{ND}(y) > 0$, $DCE_{D}(y \mid d) > 0 \forall d$

We generate data such that there is a positive treatment effect for all latent strata and, thus, a positive effect of the treatment for the ND patients (see the true model values in Table 4). To simulate such a situation, we first draw I_i^{ND} from a Bernoulli $(p(\mathbf{X}_i))$, where

$$p(\boldsymbol{X}_i) = \frac{\exp(\gamma_0 + \boldsymbol{X}_i'\boldsymbol{\gamma})}{1 + \exp(\gamma_0 + \boldsymbol{X}_i'\boldsymbol{\gamma})}; \qquad (17)$$

than, we specify the model for the potential outcomes as follows:

$$D_i(1) \mid \mathbf{I}_i^{\mathrm{ND}} = 0 \sim \mathrm{Weibull}(\alpha_D, e^{-(\beta_D + \mathbf{X}_i' \boldsymbol{\eta}_D)/\alpha_D})$$
(18)

$$Y_i(1) \mid \mathbf{I}_i^{\mathrm{ND}} = 1, \boldsymbol{X}_i \sim \mathrm{Weibull}(\bar{\alpha}_1, e^{-(\bar{\beta}_1 + \boldsymbol{X}_i' \bar{\boldsymbol{\eta}}_1)/\bar{\alpha}_1})$$
(19)



Figure 2: *Scenario I.* Kaplan-Meier curves for treated (blue) and controls (red), estimated using the potential outcomes' complete simulated data (one sample).

$$Y_i(0) \mid \mathbf{I}_i^{\text{ND}} = 1, \boldsymbol{X}_i \sim \text{Weibull}(\bar{\alpha}_0, e^{-(\bar{\beta}_0 + \boldsymbol{X}_i' \bar{\boldsymbol{\eta}}_0)/\bar{\alpha}_0})$$
(20)

$$Y_{i}(1) \mid I_{i}^{\text{ND}} = 0, D(1), \boldsymbol{X}_{i} \sim \text{tWeibull}_{D_{i}(1)}(\alpha_{1}, e^{-(\beta_{1} + \boldsymbol{X}_{i}'\boldsymbol{\eta}_{1} + \delta \log(D_{i}(1)))/\alpha_{1}})$$
(21)

$$Y_i(0) \mid \mathbf{I}_i^{\mathrm{ND}} = 0, D(1), \boldsymbol{X}_i \sim \mathrm{Weibull}(\alpha_0, e^{-(\beta_0 + \boldsymbol{X}_i' \boldsymbol{\eta}_0 + \delta \log(D_i(1)))/\alpha_0})$$
(22)

In Equation (21), tWeibull_{$D_i(1)$} stands for left truncated Weibull with truncation parameter $D_i(1)$.

The Kaplan-Meier estimated using the potential outcomes' complete data are shown in Figures 2a and 2b, whereas Figure 3 shows the observed survival curves.

5.1.2 Scenario II: $ACE_{ND} > 0$, $ACE_{D} = 0$, $DCE_{ND}(y) > 0$, $DCE_{D}(y \mid d) = 0 \forall d$

We simulate the data such that the principal causal effects for D patients are zero. However, the treatment has a positive effect on ND patients; the overall ITT effect is positive. In order to mimic such a situation, as in Scenario I, we simulate the principal stratum membership and the time-to-discontinuation as in Equations (17) and (18), respectively, and the potential outcomes for ND patients as in Equations (19) and (20). Then, we generate the potential outcomes under investiga-tional treatment and under control for D patients under the assumption that they are independent and identically distributed conditionally on the potential time to discontinuation and the covariates.



Figure 3: *Scenario I.* Kaplan-Meier curves for treated (blue) and controls (red), estimated using the simulated data (one sample).

Specifically, we assume that they both follow the following truncated Weibull distribution:

$$\{Y_{i}(1) \mid \mathbf{I}_{i}^{\mathrm{ND}} = 0, D(1), \boldsymbol{X}_{i}\}, \{Y_{i}(0) \mid \mathbf{I}_{i}^{\mathrm{ND}} = 0, D(1), \boldsymbol{X}_{i}\} \stackrel{iid}{\sim} \mathrm{tWeibull}_{D_{i}(1)}(\alpha, e^{-(\beta + \boldsymbol{X}_{i}'\boldsymbol{\eta} + \delta \log(D_{i}(1)))/\alpha})$$
(23)

Here the two potential outcomes have the same conditional distribution for each D patient. The Kaplan-Meier curves based on potential outcomes' complete data (Figures 4a and 4b) clearly show no effect for the D patients.

It is not possible to grasp that difference without resorting to the principal stratum strategy; the observed survival curves in Figure 5 show a positive ITT effect.

5.2 Modeling details and prior specification

We correctly specify the model for the the principal stratum membership and the discontinuation time assuming that I_i^{ND} follows a Bernoulli distribution with probability parameter

$$p(\boldsymbol{X}_i) = \frac{\exp(\gamma_0 + \boldsymbol{X}_i'\boldsymbol{\gamma})}{1 + \exp(\gamma_0 + \boldsymbol{X}_i'\boldsymbol{\gamma})}, \quad \boldsymbol{\theta}^{\bar{\mathbb{D}}} = (\gamma_0, \boldsymbol{\gamma}) \in \mathbb{R}^{K+1},$$
(24)



Figure 4: *Scenario II.* Kaplan-Meier curves for treated (blue) and controls (red), estimated using the potential outcomes' complete data (one sample).



Figure 5: *Scenario II.* Kaplan-Meier curves for treated (blue) and controls (red), estimated using the observed data (one sample).

and modelling the potential discontinuation under treatment as follows:

$$D_i(1)|\mathbf{I}_i^{\mathrm{ND}} = 0, \boldsymbol{X}_i \sim \mathrm{Weibull}(\alpha_D, e^{-(\beta_D + \boldsymbol{X}_i' \boldsymbol{\eta}_D)/\alpha_D}), \quad \boldsymbol{\theta}^D = (\alpha_D, \beta_D, \boldsymbol{\eta}_D)$$
(25)

with $\alpha_D \in \mathbb{R}^+$, $\beta_D \in \mathbb{R}$, and $\eta_D \in \mathbb{R}^K$.

Then, independently of how we simulated data, to estimate the causal effects under any scenario, we model the potential outcomes as follows:

$$\psi_{\bar{1}}(\cdot;\bar{\boldsymbol{\theta}}^{1},\boldsymbol{X}_{i}) = \text{Weibull}(\bar{\alpha}_{1},e^{-(\bar{\beta}_{1}+\boldsymbol{X}_{i}'\bar{\boldsymbol{\eta}}_{1})/\bar{\alpha}_{1}}), \quad \bar{\boldsymbol{\theta}}^{1} = (\bar{\alpha}_{1},\bar{\beta}_{1},\bar{\boldsymbol{\eta}}_{1})$$
(26)

$$\psi_{\bar{0}}(\cdot;\bar{\boldsymbol{\theta}}^{0},\boldsymbol{X}_{i}) = \text{Weibull}(\bar{\alpha}_{0}, e^{-(\bar{\beta}_{0}+\boldsymbol{X}_{i}'\bar{\boldsymbol{\eta}}_{0})/\bar{\alpha}_{0}}), \quad \bar{\boldsymbol{\theta}}^{0} = (\bar{\alpha}_{0}, \bar{\beta}_{0}, \bar{\boldsymbol{\eta}}_{0})$$
(27)

$$\psi_1(\cdot;\boldsymbol{\theta}^1, \boldsymbol{X}_i, D_i(1)) = \text{tWeibull}_{D_i(1)}(\alpha_1, e^{-(\beta_1 + \boldsymbol{X}_i'\boldsymbol{\eta}_1 + \delta \log(D_i(1)))/\alpha_1}), \ \boldsymbol{\theta}^1 = (\alpha_1, \beta_1, \boldsymbol{\eta}_1, \delta)$$
(28)

$$\psi_0(\cdot;\boldsymbol{\theta}^0, \boldsymbol{X}_i, D_i(1)) = \text{Weibull}(\alpha_0, e^{-(\boldsymbol{\beta}_0 + \boldsymbol{X}_i' \boldsymbol{\eta}_0 + \delta \log(D_i(1)))/\alpha_0}), \quad \boldsymbol{\theta}^0 = (\alpha_0, \beta_0, \boldsymbol{\eta}_0, \delta)$$
(29)

The above model is a correct specification of the model under Scenario I. Under Scenario II, the model is misspecified due to Equation (29): a truncated Weibull, rather than the Weibull, is the true underlying model, and the parameters of the model are the same as those in Equation (28). The parameter δ in Equations (28) and (29) capture the dependence between the potential outcomes and the potential discontinuation time under treatment. Note that the dependence between $Y_i(0)$ and $D_i(1)$ is not identifiable since we never observe the discontinuation behaviour of a unit assigned to the control. Hence, we let $Y_i(1)$ and $Y_i(0)$ depend on the common parameter δ , similarly as in Mattei et al. [2023a].

Concerning the prior specification, we assume multivariate Normal priors for all parameters playing the role of covariates' coefficients and intercepts; we assume Gamma priors for Weibulls' shape parameters. Further details and the hyperparameters specification can be found in the Supplementary Material.

5.3 Simulation study

We simulate 100 samples under each scenario described in Section 5.1 to evaluate the performance of our method in repeated sampling in terms of coverage.Results in Table 3 show how often the 95% Highest Posterior Density intervals cover the "true" values of the effects, i.e., the values computed using the complete simulated data. For the sake of brevity, we show results for the average causal effects only.

As stated in Section 5.2, the model we use to estimate the causal effects is correctly specified under Scenario I; in such a case, the 95% HPD coverage is good (Table 3, row 1).Under Scenario II, the model is misspecified; thus, as we expected, the coverage worsens (Table 3, row 3).

However, the results under Scenario II are superior to those obtained estimating the model without covariates (Table 3, row 4). Intuitively, proper utilization of auxiliary variables provides extra dimensions to better predict the missing principal strata membership; recent results on mixture models show that a multivariate analysis improves the efficiency of estimators [Mercatanti et al., 2015]. In this case, the inclusion of covariates may mitigate the impact of the model misspecification.

These results show how crucial it is to include covariates available that are also good predictors of the potential outcomes and of the latent principal stratum membership in the context of treatment discontinuation in RCTs.

In the next paragraph, we show the performance of the model on one data set per scenario.

Table 3: 95% High Posterior Density coverage of the *true* values expressed as a relative frequency over a number of samples = 100.

Scenario	ITT	$ACE_{\rm ND}$	$ACE_{\rm D}$	$ACE_{\rm D}(1)$	$ACE_{\rm D}(2)$	$ACE_{\rm D}(3)$	$ACE_{\rm D}(4)$
Ι	0.95	0.92	0.92	0.93	0.93	0.93	0.93
I w/o covariates	0.90	0.92	0.92	0.76	0.72	0.69	0.68
II	0.76	0.81	0.75	0.94	0.85	0.72	0.41
II w/o covariates	0.81	0.77	0.58	0.70	0.66	0.55	0.38

5.4 Estimation of causal effects

5.4.1 Scenario I.

Table 4 shows the results for the principal average causal effects and for the ITT effect computed as the weighted average of the principal ACE's. The posterior means of the effects are all positive and very close to the simulated value.

Table 4: *Scenario I.* Posterior mean and 95% Highest Posterior Density interval of the percentage of ND patients and the population causal estimands considered.

	True model value	Posterior Mean	95% HPD
$\pi_{\rm ND}$	0.73	0.73	[0.69; 0.78]
$\pi_{\rm ND}ACE_{\rm ND} + (1 - \pi_{\rm ND})ACE_{\rm D}$	4.24	4.49	[3.42; 5.56]
$ACE_{\rm ND}$	4.92	5.20	[3.92; 6.78]
ACED	2.40	2.52	[0.67; 4.30]

Figure 6 shows the population average causal effect for D patients as a function of the discontinuation time. Note that patients who receive the treatment for longer may benefit more from the new investigational drug even though they will experience an AE at a certain time.

Figures 7 and 8 show the principal survival differences as we defined them in Section 3.2. As we expect, both $DCE_{ND}(y)$ and the $DCE_{D}(y \mid d)$ for each d are first concave, and then, after the peak, they flex and become convex. Such behaviour indicates that the survival curve under control decreases much faster than the one under treatment.

5.4.2 Scenario II

Table 5 summarises the results obtained under Scenario II in terms of principal causal effects and ITT effect computed as the weighted average of the principal ACE's. The overall ITT effect is positive; the principal stratification approach allows us to highlight that the stratum of ND patients leads to such a result. In fact, the $ACE_{\rm ND}$ is positive, whereas we cannot reject the hypothesis of no causal effect for D patients since the 95% Highest Posterior Density interval of $ACE_{\rm D}$ covers the zero.

The misspecification of the model leads to more bias as the discontinuation time gets longer (see Figure 9). However, we remind that our simulated data mimic the data in Table 1, where about



Figure 6: Scenario I. $ACE_D(d)$ as a function of the potential discontinuation time D(1) = d. The posterior mean (dotted line) is close to the simulated value (solid line), which is included in the 95% Highest Posterior Density interval (grey shade).



Figure 7: Scenario I. Principal survival difference at time y of ND patients, DCE_{ND} . The posterior mean (dotted line) is close to the simulated value (solid line), which is always included in the 95% Highest Posterior Density interval (grey shade).



Figure 8: Scenario I. Principal survival difference at time y of D patients, $DCE_D(y \mid d)$, for different potential discontinuation time D(1) = d (in different colours).

Table 5: *Scenario II*. Posterior mean and 95% Highest Posterior Density interval of the percentage of ND patients and the population causal estimands considered.

	True model value	Posterior Mean	$95\%~\mathrm{HPD}$
$\pi_{ m ND}$	0.73	0.72	[0.68; 0.77]
$\pi_{\rm ND}ACE_{\rm ND} + (1 - \pi_{\rm ND})ACE_{\rm D}$	4.18	4.24	[2.99; 5.55]
$ACE_{\rm ND}$	5.72	5.40	[3.36; 7.23]
$ACE_{\rm D}$	0.00	1.14	[-2.66; 6.02]



Figure 9: Scenario II. $ACE_D(d)$, as a function of the potential discontinuation time D(1) = d. The posterior mean (dotted line) diverges from the 0 (solid line) as d increases, which is covered by the 95% Highest Posterior Density interval (grey shade) though.

75% of patients discontinue within the first 4 months. Yet, the $ACE_{\rm D}(d)$ Highest Posterior Density (HPD) interval at the 95% credibility level shown in Figure 9 is widely covering the 0.

Figures 10 and 11 show the principal survival differences for ND and D patients, respectively. As for the principal ACE's, there is evidence of a positive treatment effect on the PFS of the ND patients. Indeed, as in Scenario I, $DCE_{ND}(y)$ shows a peak and then slowly goes to zero. However, here the Highest Posterior Density intervals are much wider, indicating more uncertainty deriving from the misspecification of the model. $DCE_{D}(y \mid d)$ sharply go to zero, suggesting there is no significant treatment effect for the D patients.



Figure 10: Scenario II. Principal survival difference of ND patients, DCE_{ND} .

6 The role of covariates: Characterisation of the principal strata

We previously stressed the role of covariates as predictors that allow more precise estimates of the causal effects in the simulation study in Section 5.3. The results are in line with the literature. In a principal stratification analysis, even under randomisation, the use of covariates improves inference by helping the prediction of missing potential outcomes, and thus the identification of the principal causal effects [see Gilbert and Hudgens, 2008, Grilli and Mealli, 2008, Ding et al., 2011, Long and Hudgens, 2013, Mercatanti et al., 2015, Mealli and Pacini, 2013, Jiang and Ding, 2021].

Here, we highlight the importance of the covariates from a different point of view, emphasising how our approach may inform about the risk of AEs and makes the characterisation of the patients' behaviour natural in terms of the patient's baseline features. Indeed, we may be interested in profiling the patients in the different principal strata in terms of the covariates; so we can better predict whether a patient will discontinue the treatment and when. For a likelihood-based approach to this issue, see Frumento et al. [2012].



Figure 11: Scenario II. Principal survival difference at time y of D patients, $DCE_D(y \mid d)$, for different potential discontinuation time D(1) = d (in different colours).



Figure 12: Distribution of X_1 by latent stratum - 'Never Discontinue' refers to those patients whose $I_i^{\text{ND}} = 1$; 'Discontinue late' and 'Discontinue early' refer to patients whose $D_i(1) \ge \text{median}(D_i(1))$ and $D_i(1) < \text{median}(D_i(1))$, respectively.

We investigate the distribution of the covariates within different principal strata, e.g., ND patients, *early* D patients and *late* D patients. The early D patients are those discontinuing before the median time of discontinuation, whereas the late D patients discontinue after.

The availability of posterior samples of memberships and discontinuation time make it straightforward to characterise the principal strata. Figures 12-14 show the distributions of the covariates used in our analyses with respect to the patients' membership.

ND patients are characterised by lower values of X_1 (Figure 12). However, given that one would discontinue the treatment, the lower the value of X_1 , the later the discontinuation.

The higher the probability that X_2 or X_3 is equal to 1, the more likely the patient would be a ND one. However, if one discontinues, those with a higher probability of $X_3 = 1$ discontinue sooner; the association of X_2 to the discontinuation time is not strong.

The results are reasonable and consistent with the assumptions used in simulating the data.

7 Discussion

This paper addresses a relevant but challenging clinical question. A novel treatment (administered in combination with the standard of care) is more likely to trigger AEs leading to discontinuation



Figure 13: Distribution of X_2 by latent stratum - 'Never Discontinue' refers to those patients whose $I_i^{ND} = 1$; 'Discontinue late' and 'Discontinue early' refer to patients whose $D_i(1) \ge \text{median}(D_i(1))$ and $D_i(1) < \text{median}(D_i(1))$, respectively.



Figure 14: Distribution of X_3 by latent stratum - 'Never Discontinue' refers to those patients whose $I_i^{ND} = 1$; 'Discontinue late' and 'Discontinue early' refer to patients whose $D_i(1) \ge \text{median}(D_i(1))$ and $D_i(1) < \text{median}(D_i(1))$, respectively.

of the novel component while continuing the standard of care alone. To assess the treatment effect depending on the discontinuation status, we adopt a principal stratification approach, classifying patients according to their potential discontinuation time under treatment. Suppose a trial shows a clinically meaningful overall treatment effect based on ITT analysis; then naturally, one may be interested in the treatment effect in those who adhere to the treatment but also in those who discontinue the treatment. This would help a better understanding of the drug mechanism (e.g. whether taking only some doses initially may prove a longer-lasting benefit even after early discontinuation) and will provide a more complete picture for clinical decision-making. For instance, whether early treatment discontinuation leads to reduced or null treatment benefit; whether treatment discontinuation depends on specific baseline covariates; and so on, all constitute clinically relevant information that can be used in the risk and benefit assessment of a new treatment for an individual patient.

For inference, we developed a flexible parametric Bayesian model that takes into account (i) whether or not a patient is a patient who would discontinue the treatment if assigned to it, (ii) that time to discontinuation is a continuous variable, and (iii) that both discontinuation and efficacy endpoints are subject to administrative censoring. In the motivating application, we used specific parametric models; however, the approach is more general and can also be implemented with alternative model specifications. All model components allow for the inclusion of baseline covariates, which makes the parametric assumptions more plausible and improves the prediction of the missing potential outcomes. It also potentially allows us to characterize the D patients by discontinuation on the drug and has strong implications for further development: If AEs are associated to certain baseline characteristics and if patients who discontinue the treatment have a reduced treatment effect, one could investigate an optimized dosing regimen or improved AE management guideline for these patients in further research.

Our approach enables us to decompose the ITT effect into the actual treatment effect for ND patients and the effects of initiating the treatment for D ones. Hence, it allows us to evaluate whether, e.g., a positive ITT effect results from either positive effects for each type of patients or only for some specific subgroups.

In this work, we assume that covariates that are good predictors of outcome variables (time to

event, discontinuation status, and time to discontinuation) are available. In practice, covariates or prognostic factors impacting time to progression or death are usually well discussed, recognized, and collected for specific disease areas, while baseline covariates that may impact the discontinuation status may not always be clear and readily available, especially for rare disease and novel treatment (as well as its chosen dosing regimen). At the design stage, it is hence important to assess potential covariates (based on earlier trials or clinical or mechanistic understanding) and make those covariates part of the data collection. Our simulation study shows that the model performance strongly improves by including appropriate covariates in the analysis.

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Supplementary material for

"Evaluating causal effects on time-to-event outcomes in an RCT in Oncology with treatment discontinuation due to adverse events"

A Model specification

We describe in detail the model specified in the main text.

We assume that the probability of being an ND patient is

$$p(\boldsymbol{X}_i) = \frac{\exp(\gamma_0 + \boldsymbol{X}'_i \boldsymbol{\gamma})}{1 + \exp(\gamma_0 + \boldsymbol{X}'_i \boldsymbol{\gamma})}, \quad \boldsymbol{\theta}^{\bar{\mathbb{D}}} = (\gamma_0, \boldsymbol{\gamma}) .$$
(A. 1)

Given the principal strata one belongs to, the potential discontinuation time under treatment is:

$$D_{i}(1)|\mathbf{I}_{i}^{\mathrm{ND}}, \boldsymbol{X}_{i} \begin{cases} = \bar{\mathbb{D}} & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{D}(\cdot; \boldsymbol{\theta}^{D}, \boldsymbol{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 . \end{cases}$$
(A. 2)

We denote with $f_{D(1)}(d|\mathbf{X}_i, \boldsymbol{\theta}^D)$ and $G_{D(1)}(d|\mathbf{X}_i \boldsymbol{\theta}^D)$ the density and survival functions for the discontinuation time of who discontinued, respectively. In the case of the Weibull specification,

$$f_{D(1)}(d \mid \boldsymbol{X}, \boldsymbol{\theta}_D) = \alpha_D y^{\alpha_D - 1} \exp\{\beta_D + \boldsymbol{X}'_i \boldsymbol{\eta}_D - e^{\beta_D + \boldsymbol{X}'_i \boldsymbol{\eta}_D} y^{\alpha_D}\},$$

$$G_{D(1)}(d \mid \boldsymbol{X}, \boldsymbol{\theta}_D) = \exp\{-e^{\beta_D + \boldsymbol{X}'_i \boldsymbol{\eta}_D} y^{\alpha_D}\}, \quad \boldsymbol{\theta}^D = (\alpha_D, \beta_D, \boldsymbol{\eta}_D)$$
(A. 3)

The potential outcome under treatment $Y_i(1)$, given the discontinuation status $D_i(1)$ and the covariates, is

$$Y_{i}(1)|\mathbf{I}_{i}^{\mathrm{ND}}, D_{i}(1), \boldsymbol{X}_{i} \begin{cases} \sim \psi_{\bar{1}}(\cdot; \boldsymbol{\bar{\theta}}^{1}, \boldsymbol{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{1}(\cdot; \boldsymbol{\theta}^{1}, \boldsymbol{X}_{i}, D_{i}(1)) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 . \end{cases}$$
(A. 4)

For ND patients, the Weibull density and the survival functions are

$$f_{Y(1)}^{\bar{\mathbb{D}}}(y \mid \boldsymbol{X}, \bar{\boldsymbol{\theta}}_{1}) = \bar{\alpha}_{1} y^{\bar{\alpha}_{1}-1} \exp\{\bar{\beta}_{1} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{1} - e^{\bar{\beta}_{1} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{1}} y^{\bar{\alpha}_{1}}\},$$

$$G_{Y(1)}^{\bar{\mathbb{D}}}(y \mid \boldsymbol{X}, \bar{\boldsymbol{\theta}}_{1}) = \exp\{-e^{\bar{\beta}_{1} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{1}} y^{\bar{\alpha}_{1}}\}, \quad \bar{\boldsymbol{\theta}}^{1} = (\bar{\alpha}_{1}, \bar{\beta}_{1}, \bar{\boldsymbol{\eta}}_{1}),$$
(A. 5)

respectively. Yet, for D patients, the left truncated Weibull density and survival functions are

$$f_{Y(1)}(y \mid d, \mathbf{X}, \boldsymbol{\theta}_{1}) = \alpha_{1} y^{\alpha_{1}-1} \exp\{\beta_{1} + \mathbf{X}_{i}' \boldsymbol{\eta}_{1} + \delta \log D(1) + e^{\beta_{1} + \mathbf{X}_{i}' \boldsymbol{\eta}_{1} + \delta \log D(1)} (d^{\alpha_{1}} - y^{\alpha_{1}})\} \mathbb{I}_{d \leq y},$$

$$G_{Y(1)}(y \mid d, \mathbf{X}, \boldsymbol{\theta}_{1}) = \exp\{e^{\beta_{1} + \mathbf{X}_{i}' \boldsymbol{\eta}_{1} + \delta \log D(1)} (d^{\alpha_{1}} - y^{\alpha_{1}})\} \mathbb{I}_{d \leq y}, \quad \boldsymbol{\theta}^{1} = (\alpha_{1}, \beta_{1}, \boldsymbol{\eta}_{1}),$$
(A. 6)

respectively.

We assume that the potential outcome under control $Y_i(0)$ is independent of $Y_i(1)$ given $D_i(1)$ and the covariates, i.e.,

$$Y_{i}(0)|\mathbf{I}_{i}^{\mathrm{ND}}, D_{i}(1), \boldsymbol{X}_{i} \begin{cases} \sim \psi_{\bar{0}}(\cdot; \bar{\boldsymbol{\theta}}^{0}, \boldsymbol{X}_{i}) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 1 \\ \sim \psi_{0}(\cdot; \boldsymbol{\theta}^{0}, \boldsymbol{X}_{i}, D_{i}(1)) & \text{if } \mathbf{I}_{i}^{\mathrm{ND}} = 0 . \end{cases}$$
(A. 7)

The Weibull densities of $Y_i(0)|\mathbf{I}_i^{\text{ND}}, D_i(1), \mathbf{X}_i$ are

$$f_{Y(0)}^{\bar{\mathbb{D}}}(y \mid \boldsymbol{X}, \bar{\boldsymbol{\theta}}_{0}) = \bar{\alpha}_{1} y^{\bar{\alpha}_{0}-1} \exp\{\bar{\beta}_{0} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{0} - e^{\bar{\beta}_{1} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{0}} y^{\bar{\alpha}_{0}}\},$$

$$G_{Y(0)}^{\bar{\mathbb{D}}}(y \mid \boldsymbol{X}, \bar{\boldsymbol{\theta}}_{0}) = \exp\{-e^{\bar{\beta}_{1} + \boldsymbol{X}_{i}' \bar{\boldsymbol{\eta}}_{0}} y^{\bar{\alpha}_{0}}\}, \quad \bar{\boldsymbol{\theta}}^{0} = (\bar{\alpha}_{0}, \bar{\beta}_{0}, \bar{\boldsymbol{\eta}}_{0})$$
(A. 8)

for those who would never discontinue; yet, for those who would discontinue if assigned to the treatment, they are:

$$f_{Y(1)}(y \mid d, \mathbf{X}, \boldsymbol{\theta}_{1}) = \alpha_{0} y^{\alpha_{0}-1} \exp\{\beta_{0} + \mathbf{X}_{i}' \boldsymbol{\eta}_{0} + \delta \log D(1) - e^{\beta_{0} + \mathbf{X}_{i}' \boldsymbol{\eta}_{1} + \delta \log D(1)} y^{\alpha_{0}}\},$$

$$G_{Y(1)}(y \mid d, \mathbf{X}, \boldsymbol{\theta}_{1}) = \exp\{-e^{\beta_{0} + \mathbf{X}_{i}' \boldsymbol{\eta}_{1} + \delta \log D(1)} y^{\alpha_{0}}\}, \quad \boldsymbol{\theta}^{0} = (\alpha_{0}, \beta_{0}, \boldsymbol{\eta}_{0}).$$
(A. 9)

B Priors specification

We assume multivariate Normal priors for all parameters playing the role of covariates' coefficients and intercepts; yet, we assume Gamma priors for Weibulls' shape parameters.

$$(\gamma_0, \boldsymbol{\gamma}) \sim \mathrm{N}(\mathbf{0}, \Sigma_{\bar{\mathbb{D}}})$$
 (B. 1)

$$\alpha_D \sim \text{Gamma}(a, b), \quad \beta_D \sim N(0, \sigma_D^2) \quad \boldsymbol{\eta}_D) \sim N(\mathbf{0}, \Sigma_D)$$
(B. 2)

$$\bar{\alpha}_1 \sim \text{Gamma}(\bar{a}_1, \bar{b}_1), \quad \bar{\beta}_1 \sim N(0, \sigma_1^2)$$
 (B. 3)

$$\alpha_1 \sim \text{Gamma}(a_1, b_1), \quad \beta_1 \sim \mathcal{N}(0, \sigma_1^2)$$
 (B. 4)

$$\bar{\alpha}_0 \sim \text{Gamma}(\bar{a}_0, \bar{b}_0), \quad \bar{\beta}_0 \sim N(0, \sigma_{\bar{0}}^2)$$
 (B. 5)

$$\alpha_0 \sim \text{Gamma}(a_0, b_0), \quad \beta_0 \sim \mathcal{N}(0, \sigma_0^2)$$
 (B. 6)

$$\bar{\boldsymbol{\eta}}_1 = \boldsymbol{\eta}_1 = \bar{\boldsymbol{\eta}}_0 = \boldsymbol{\eta}_0 \equiv \boldsymbol{\eta}_Y \sim \mathrm{N}(\boldsymbol{0}, \boldsymbol{\Sigma}_Y)$$
 (B. 7)

$$\delta \sim \mathcal{N}(0, \sigma_{\delta}^2) \tag{B. 8}$$

The results shown in the main text are obtained setting (i) all Gammas' shape parameters equal to 0.5, (ii) all Gammas' scale parameters equal to 0.5, (iii) all variances $\sigma^2 = 10^2$, and (iv) variancecovariance matrices Σ as diagonal matrices with non-zero elements equal to 5². The results are quite robust to hyperparameters' specifications.

C Posterior distribution

We write the posterior using the observed data likelihood:

$$\begin{aligned} \pi(\boldsymbol{\theta} \mid \boldsymbol{X}, \boldsymbol{Z}, \boldsymbol{C}, \tilde{\boldsymbol{D}}^{\text{obs}}, \tilde{\boldsymbol{Y}}^{\text{obs}}) &\propto \pi(\boldsymbol{\theta}^{\overline{\mathbb{D}}}) \pi(\boldsymbol{\theta}^{D}) \pi(\boldsymbol{\theta}^{1}) \pi(\boldsymbol{\theta}^{0}) \pi(\boldsymbol{\theta}^{0}) \\ &\times \prod_{i:Z_{i}=1, \tilde{Y}_{i}^{\text{obs}}=Y_{i}^{\text{obs}}, \tilde{D}_{i}^{\text{obs}}=C_{i}} p(\boldsymbol{X}_{i}) f_{Y(1)}^{\overline{\mathbb{D}}}(Y_{i}^{\text{obs}} \mid \boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{1}) \\ &\times \prod_{i:Z_{i}=1, \tilde{Y}_{i}^{\text{obs}}=C_{i}, \tilde{D}_{i}^{\text{obs}}=D_{i}^{\text{obs}}} [1 - p(\boldsymbol{X}_{i})] f_{D(1)}(D_{i}^{\text{obs}} \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) G_{Y(1)}(C_{i} \mid D_{i}^{\text{obs}}, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{1}) \\ &\times \prod_{i:Z_{i}=1, \tilde{Y}_{i}^{\text{obs}}=Y_{i}^{\text{obs}}, \tilde{D}_{i}^{\text{obs}}=D_{i}^{\text{obs}}} [1 - p(\boldsymbol{X}_{i})] f_{D(1)}(D_{i}^{\text{obs}} \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) f_{Y(1)}(Y_{i}^{\text{obs}} \mid D_{i}^{\text{obs}}, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{1}) \\ &\times \prod_{i:Z_{i}=1, \tilde{Y}_{i}^{\text{obs}}=C_{i}, \tilde{D}_{i}^{\text{obs}}=D_{i}^{\text{obs}}} [1 - p(\boldsymbol{X}_{i})] f_{D(1)}(D_{i}^{\text{obs}} \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) f_{Y(1)}(Y_{i}^{\text{obs}} \mid D_{i}^{\text{obs}}, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{1}) \\ &\times \prod_{i:Z_{i}=1, \tilde{Y}_{i}^{\text{obs}}=C_{i}, \tilde{D}_{i}^{\text{obs}}=C_{i}} p(\boldsymbol{X}_{i}) G_{Y(1)}^{\overline{\mathbb{D}}}(C_{i} \mid \boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{1}) + [1 - p(\boldsymbol{X}_{i})] G_{D(1)}(C_{i} \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) \\ &\times \prod_{i:Z_{i}=0, \tilde{Y}_{i}^{\text{obs}}=Y_{i}^{\text{obs}}} \left[p(\boldsymbol{X}_{i}) f_{Y(0)}^{\overline{\mathbb{D}}}(Y_{i}^{\text{obs}} \mid \boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{0}) + \\ [1 - p(\boldsymbol{X}_{i})] \int_{\mathbb{R}^{+}} f_{Y(0)}(Y_{i}^{\text{obs}} \mid D_{i}(1) = d, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) f_{D(1)}(d \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) \, \mathrm{d}d \right \right] \\ &\times \prod_{i:Z_{i}=0, \tilde{Y}_{i}^{\text{obs}}=C_{i}} \left[p(\boldsymbol{X}_{i}) G_{Y(0)}^{\overline{\mathbb{D}}}(C_{i} \mid \boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{0}) + \\ [1 - p(\boldsymbol{X}_{i})] \int_{\mathbb{R}^{+}} G_{Y(0)}(C_{i} \mid D_{i}(1) = d, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{0}) f_{D(1)}(d \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) \, \mathrm{d}d \right \right] \end{aligned}$$

Given the intractability of the observed data likelihood due to the presence of infinite mixtures, following Mattei et al. [2023a], we include a data augmentation step simulating $D_i(1)$ for units assigned to the control arm. We obtain the following complete data posterior distribution:

$$P(\boldsymbol{\theta}|\boldsymbol{X}, \boldsymbol{Z}, \boldsymbol{C}, \tilde{\boldsymbol{D}}^{\text{obs}}, \tilde{\boldsymbol{Y}}^{\text{obs}}, \boldsymbol{D}(1), \boldsymbol{Y}) \propto P(\boldsymbol{\theta}) \mathcal{L}(\boldsymbol{\theta}|\boldsymbol{X}, \boldsymbol{Z}, \boldsymbol{C}, \tilde{\boldsymbol{D}}^{\text{obs}}, \tilde{\boldsymbol{Y}}^{\text{obs}}, \boldsymbol{D}(1), \boldsymbol{Y})$$

$$\propto \pi(\boldsymbol{\theta}^{\overline{\mathbb{D}}}) \times \pi(\boldsymbol{\theta}^{D}) \times \pi(\bar{\boldsymbol{\theta}}^{1}) \times \pi(\boldsymbol{\theta}^{1}) \times \pi(\bar{\boldsymbol{\theta}}^{0}) \times \pi(\boldsymbol{\theta}^{0})$$

$$\times \prod_{i:Z_{i}=1,D_{i}(1)=\overline{\mathbb{D}}} p(\boldsymbol{X}_{i}) f_{Y(1)}^{\overline{\mathbb{D}}}(Y_{i}^{\text{obs}}|\boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{1})^{\mathbb{I}\{Y_{i}^{\text{obs}} \leq C_{i}\}} G_{Y(1)}^{\overline{\mathbb{D}}}(C_{i}|\boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{1})^{\mathbb{I}\{Y_{i}^{\text{obs}} > C_{i}\}}$$

$$\times \prod_{i:Z_{i}=1,D_{i}(1)\in\mathbb{R}^{+}} [1 - p(\boldsymbol{X}_{i})] G_{D(1)}(C_{i}|\boldsymbol{X}_{i}, \boldsymbol{\theta}^{D})^{\mathbb{I}\{D_{i}^{\text{obs}} > C_{i}\}}$$

$$\cdot \left[f_{D(1)}(D_{i}^{\text{obs}}|\boldsymbol{X}_{i}, \boldsymbol{\theta}^{D}) f_{Y(1)}(Y_{i}^{\text{obs}}|D_{i}^{\text{obs}}, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{1})^{\mathbb{I}\{Y_{i}^{\text{obs}} \leq C_{i}\}} G_{Y(1)}(C_{i}|D_{i}^{\text{obs}}, \boldsymbol{X}_{i}, \boldsymbol{\theta}^{1})^{\mathbb{I}\{Y_{i}^{\text{obs}} > C_{i}\}} \right]^{\mathbb{I}\{D_{i}^{\text{obs}} \leq C_{i}\}}$$

$$\times \prod_{i:Z_{i}=0,D_{i}(1)=\overline{\mathbb{D}}} p(\boldsymbol{X}_{i}) f_{Y(0)}^{\overline{\mathbb{D}}}(Y_{i}^{\text{obs}}|\boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{0})^{\mathbb{I}\{Y_{i}^{\text{obs}} \leq C_{i}\}} G_{Y(0)}^{\overline{\mathbb{D}}}(C_{i}|\boldsymbol{X}_{i}, \bar{\boldsymbol{\theta}}^{0})^{\mathbb{I}\{Y_{i}^{\text{obs}} > C_{i}\}}$$

$$\times \prod_{i:Z_{i}=0,D_{i}(1)\in\mathbb{R}^{+}} [1 - p(\boldsymbol{X}_{i})] f_{D(1)}(D_{i}(1)|\boldsymbol{X}_{i}, \boldsymbol{\theta}^{D})$$

$$\cdot f_{Y(0)}(Y_{i}^{\text{obs}}|D_{i}(1), \boldsymbol{X}_{i}, \boldsymbol{\theta}^{0})^{\mathbb{I}\{Y_{i}^{\text{obs}} \leq C_{i}\}} G_{Y(0)}(C_{i}|D_{i}(1), \boldsymbol{X}_{i}, \boldsymbol{\theta}^{0})^{\mathbb{I}\{Y_{i}^{\text{obs}} > C_{i}\}}$$
(C. 2)

Once derived the full conditionals, it will be possible to draw from the posterior above using a Metropolis-within-Gibbs algorithm such as the one described in Algorithm 1.

D Algorithm description

Following Mattei et al. [2023a], we implemented a Metropolis within Gibbs with Data Augmentation to estimate the causal effects of a new investigational drug, administered in addition to the standard of care, with respect to the standard of care only. The algorithm is described by Algorithms 1 and 2.

Algorithm 1: Metropolis within Gibbs
1 Choose initial values for all the J elements of the vector $\boldsymbol{\theta}^{(0)}$;
2 Choose initial values $I_i^{\text{ND}(0)} \forall i \in \{Z_i = 0 \cup (Z_i = 1 \cap Y_i^{\text{obs}} > C_i)\};$
3 Choose initial values $D_i(1)^{(0)} \forall i \in Z_i = 0$;
4 for $t \leftarrow 1$ to T do
5 1. Data augmentation as in Algorithm 2
6 2. Parameters' update
7 for $\boldsymbol{\theta}[j] \leftarrow \boldsymbol{\theta}[1]$ to $\boldsymbol{\theta}[J]$ do
8 draw $\boldsymbol{\theta}[j]^*$ from a proposal distribution $q_t(\boldsymbol{\theta}[j]^* \boldsymbol{\theta}[j]^{t-1})$;
9 compute the acceptance ratio $\gamma_{\boldsymbol{\theta}[j]} = \min\left(1; \frac{P(\boldsymbol{\theta}[j]^* \cdot)}{P(\boldsymbol{\theta}[j]^{t-1} \cdot)} \frac{q_t(\boldsymbol{\theta}[j]^{t-1} \boldsymbol{\theta}[j]^*)}{\boldsymbol{\theta}[j]^* \boldsymbol{\theta}[j])}\right);$
10 draw $u \sim \text{Unif}(0,1)$;
11 if $u < \gamma_{\theta[j]}$ then
12 $\operatorname{set} \boldsymbol{\theta}[j]^{(t)} = \boldsymbol{\theta}[j]^*$
13 else
14 set $\boldsymbol{\theta}[j]^{(t)} = \boldsymbol{\theta}[j]^{t-1}$
15 end
16 end
17 end

Algorithm 2: Data augmentation step at iteration t

1 for $i: Z_i = 1, Y_i^{obs} > C_i$ do compute the ratio $\mathbf{2}$ $\gamma_i = \frac{p(\boldsymbol{X}_i, \boldsymbol{\theta}^{\bar{\mathbb{D}}(t)}) G_{Y(1)}^{\mathbb{D}}(Y_i^{\mathrm{obs}} | \boldsymbol{X}_i, \boldsymbol{\theta}^{1(t)})}{p(\boldsymbol{X}_i, \boldsymbol{\theta}^{\bar{\mathbb{D}}(t)}) G_{Y(1)}^{\mathbb{D}}(Y_i^{\mathrm{obs}} | \boldsymbol{X}_i, \boldsymbol{\theta}^{1(t)}) + (1 - p(\boldsymbol{X}_i, \boldsymbol{\theta}^{\bar{\mathbb{D}}(t)})) G_{D(1)}(D_i^{\mathrm{obs}} | \boldsymbol{X}_i, \boldsymbol{\theta}^{1(t)})} ;$ 3 draw $I_i^{\text{ND}(t)} \sim \text{Ber}(\gamma_i)$ $\mathbf{4}$ 5 end 6 for $i: Z_i = 0$ do draw $\mathbf{I}_{i}^{\mathrm{ND}*} \sim \mathrm{Ber}(P(\mathbf{I}_{i}^{\mathrm{ND}} \mid \boldsymbol{X}_{i}, \boldsymbol{\theta}^{\bar{\mathbb{D}}, (t-1)}));$ 7 if $I_i^{ND*} = 0$ then 8 draw $D(1)_i^* \sim \text{Weibull}(\alpha_D^{(t-1)}, \exp{(-\{\beta_D^{(t-1)} + \mathbf{X}_i' \mathbf{\eta}_D^{(t-1)}\}}/\alpha_D^{(t-1)}))$ 9 \mathbf{else} 10 set $D(1)_i^* = 0$ 11 end compute the ratio $r_i = \frac{\pi(\boldsymbol{\theta}^{(t-1)}|\mathbf{I}_i^{\mathrm{ND}*}, D_i^*, Y_i^{\mathrm{obs}}, \mathbf{X}_i)}{\pi(\boldsymbol{\theta}^{(t-1)}|\mathbf{I}_i^{\mathrm{ND}(t-1)}, D_i^{(t-1)}, Y_i^{\mathrm{obs}}, \mathbf{X}_i)}$; $\boldsymbol{I}_i = \mathbf{I}_i^{\mathrm{ND}(t-1)} = 1$ 1213 $\text{compute } \rho_i = \begin{cases} \frac{p(\mathbf{X}_i, \boldsymbol{\theta}^{\mathbb{D}(t-1)})}{(1-p(\mathbf{X}_i, \boldsymbol{\theta}^{\mathbb{D}(t-1)}))f_D(D_i^* | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})} & \text{if } \mathbf{I}_i^{\text{ND}*} = 0, \mathbf{I}_i^{\text{ND}(t-1)} = 1\\ \frac{(1-p(\mathbf{X}_i, \boldsymbol{\theta}^{\mathbb{D}(t-1)}))f_D(D_i^{(t-1)} | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})}{p(\mathbf{X}_i, \boldsymbol{\theta}^{\mathbb{D}(t-1)})} & \text{if } \mathbf{I}_i^{\text{ND}*} = 1, \mathbf{I}_i^{\text{ND}(t-1)} = 0\\ \frac{f_D(D_i^{(t-1)} | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})}{f_D(D_i^* | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})} & \text{if } \mathbf{I}_i^{\text{ND}*} = \mathbf{I}_i^{\text{ND}(t-1)} = 0\\ \frac{f_D(D_i^{(t-1)} | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})}{f_D(D_i^* | \mathbf{X}_i, \boldsymbol{\theta}^{D(t-1)})} & \text{if } \mathbf{I}_i^{\text{ND}*} = \mathbf{I}_i^{\text{ND}(t-1)} = 0\\ \text{if } u < (r_i \cdot \rho_i) \text{ then} \end{cases}$ $\mathbf{14}$ $\begin{array}{l} \mathbf{if} \ u < (r_i \cdot \rho_i) \ \mathbf{then} \\ \big| \ \ \mathbf{set} \ \mathbf{I}_i^{\mathrm{ND}(t)} = \mathbf{I}_i^{\mathrm{ND}*} \ \mathrm{and} \ D(1)_i^{(t)} = D(1)_i^* \end{array}$ $\mathbf{15}$ $\mathbf{16}$ else17set $\mathbf{I}_i^{\text{ND}(t)} = \mathbf{I}_i^{\text{ND}(t-1)}$ and $D(1)_i^{(t)} = D(1)_i^{(t-1)}$ $\mathbf{18}$ 19 \mathbf{end} 20 end

E Summary statistics for the two scenarios

Variable	Mean(proportion)	SD	Min	Q1	Median	$\mathbf{Q3}$	Max
$\overline{Z_i}$	54.0% (181/335)						
$\mathbb{I}(D_i^{\text{obs}} < C_i)$	14.93%(50/335)						
$D_i^{\rm obs}$	2.99(50/335)	2.41	0.19	1.04	2.64	3.87	11.99
$\mathbb{I}(Y_i^{\text{obs}} < C_i)$	91.64% (307/335)						
$Y^{\rm obs}$	5.16(307/335)	3.66	0.02	2.31	4.35	7.58	20.76
Continuous covariates							
X_1	63.09	10.46	28.44	55.80	63.09	70.48	91.51
Categorical covariates							
X_2	43.88% (147/335)						
<u>X</u> ₃	25.37% $(85/335)$						

Table E.1: Summary data, scenario I

Table E.2: Summary data, scenario II

Variable	Mean(proportion)	SD	Min	Q1	Median	Q3	Max
$\overline{Z_i}$	54.0% (181/335)						
$\mathbb{I}(D_i^{\text{obs}} < C_i)$	14.93%(50/335)						
$D_i^{\rm obs}$	2.99(50/335)	2.41	0.19	1.04	2.64	3.87	11.99
$\mathbb{I}(Y_i^{\text{obs}} < C_i)$	90.15% (302/335)						
$Y^{\rm obs}$	5.51(302/335)	3.87	0.01	2.36	4.87	7.84	20.76
Continuous covariates							
X_1	63.09	10.46	28.44	55.80	63.09	70.48	91.51
Categorical covariates							
X_2	43.88% (147/335)						
X_3	25.37% (85/335)						