Estimating the Complier Average Causal Effect for Exponential Survival in the Presence of Mid-Trial Switching

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Abstract: The intention-to-treat (ITT) rate ratio estimator is conservatively biased for the treatment effect among compliers (who stick with their assigned arm) when individuals switch treatment in two-arm randomised trials. In this article we propose simple ways to estimate the complier average causal effect (CACE) with mid-trial switching. The estimators use aggregate data of events and times rather than individualised data. The motivating model considers survival times as exponentially distributed conditional on whether the individual would comply with randomisation. To estimate the CACE the ante-switch treatment effect and the post-switch treatment effect amongst the compliers are combined. Furthermore, we discuss ways of estimating the counterfactual intent-to-treat (ITT) effect, which is defined as the rate ratio if switching was not permitted. This approach might be a useful alternative to CACE estimation, and so a time and event adjustment of the non-compliers data is developed. Finally, simulated switching scenarios are used to illustrate the importance of correcting for informative switching.

Keywords: Complier average causal effect, clinical trial, exponential survival, intent-to-treat, all-or-none compliance, per-protocol, switching.

1. INTRODUCTION

This report considers methods for estimating a rate-ratio treatment effect from a two-arm trial when randomisation is lost due to switching. Specifically, we consider when individuals who were randomised to control were unblinded mid-trial and offered the opportunity to switch to the treatment arm; the time of switch t_s is the same for everyone in the trial. Both arms are stratified to be composed of compliers, who stick with their assigned arm, and always-takers, who insist on treatment. The two groups are only observed in the control arm at switching. Furthermore, we take that the outcome is then either improved or worsened more than would have been expected for the treated group as a whole. We aim to estimate the rate-ratio treatment effect by comparing the survival of potential compliers in both arms. This is an example of the principal compliance framework [1, 2], where the underlying compliance class is only observed in the control arm and not the treatment arm. A motivating example of control-to-treatment switching is the BIG-1 98 trial, described in [3]. Five years from the start of the trial, women who were taking tamoxifen were unblinded and offered the opportunity to switch to letrozole. Approximately one quarter chose to cross over, and their outcome was improved more than would have been expected for the group as a whole. In other words, randomised treatment allocation was lost due to switching.

One approach to survival analysis with switching focuses on the accelerated failure time models [4-8]. These estimators might do poorly in the presence of heavy censoring due to difficulty in dealing with recensoring using accelerate failure models [5]. Other papers for all-or-none compliance estimate the CACE by subtracting out the effect of potential non-compliers from the treatment arm using the so called exclusion restriction (ER) assumption [1, 9]. This assumes equality in risk for non-compliers in both arms, which is often easy to justify for all-or-none compliance as the individuals in the two arms bear similar characteristics at the start due to randomisation. This route was taken by Cuzick and others [10], extending Sommer and Zeger [11], for binary outcomes. Their estimator has found use in real trials, including Duffy and others [12]. An extension to time-to-event data with mid-trial switching was used in Kerkhof and others [13] for a Poisson model from a prostate cancer screening trial. Cuzick and others [14] presented extensions for an all-or-none compliance Cox model. Additionally, Loeys and Goetghebeur [15] studied estimation of complier average causal effect (CACE) for proportional hazards model and White and others [9] for piecewise exponentials.

In this article, we consider estimators when for the ante and post-switch periods, aggregate survival times and number of events are recorded, being split for compliers and always-takers in the control arm post-switch. We model the survival times within a given compliance group (complier or always-taker) and arm as exponentially distributed. Simple estimators of the CACE are examined, which can be viewed as

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extensions of Cuzick and others [10]. The estimators account for mid-trial switching by combining the ante-switch and post-switch estimates of treatment effects amongst compliers. We also consider estimating the counterfactual ITT effect, which is defined as the overall risk ratio of the two arms if no switching had occurred. This approach estimates what would have happened to the observed always-takers (switchers) in control if no switching had occurred, rather than model the unobserved always-takers in the treatment arm. Thus the counterfactual ITT effect is a population-level effect which does not adjust for principal compliance. A closely related idea is the inverse probability of censoring weighting (IPCW) approach of Robins [16], which treats switching as censoring and up-weights the number of control compliers at risk, by the reciprocal of a modelled probability of being a complier. IPCW has been used in both randomised experiments, and for observational data. If the probability of potential switching in the treatment arm can be estimated consistently from observed covariates, the IPCW estimator is a consistent estimator of the marginal effect under a marginal proportional hazards model with a constant marginal effect. However, it is not possible to check the model for the probability of potential switching because there might be unmeasured confounders. Furthermore, censoring switchers is not ideal because information is lost. We consider estimators of the counterfactual ITT effect by estimating the counterfactual events and times in the control arm switchers.

Simulation examples are used to compare the relative performance of the CACE estimators and the counterfactual ITT estimator against intention-to-treat (ITT) and per-protocol (PP) methods.

2. THE EXPONENTIAL SWITCHING MODEL

The following model for switching allows compliance heterogeneity from the start by taking the population to be a mixture of compliers and always-takers (equation 1). The hazard can be written as

$$\lambda(t \mid R,Z) = \lambda_b \theta^{R+(1-R)Z\delta} \rho^Z , \quad (1)$$

where λ_b is the baseline hazard, θ is the treatment effect, R denotes randomisation (0 – control, 1 treatment), Z is the compliance group (0 complier, 1 always-taker), ρ is the always-taker effect, and δ is the indicator for having survived till switching time t_s .. We assume Z to be randomly assigned at the start with probability α and independent from all other factors. The only hazard that changes after switching is that of the control switchers (R=0, Z=1). The model is illustrated in Table **1**.

Table 1: Parameters of the Switching Model for Ante-Switch and Post-Switch

R=0	R=1
$\lambda_{0B-} = \lambda_b \rho$ $\lambda_{0A-} = \lambda_b$	$\lambda_{1B-} = \lambda_b \rho \theta$ $\lambda_{1A-} = \lambda_b \theta$
↓	
R=0	**R=1**
$\lambda_{0B+} = \lambda_b \rho \theta$ $\lambda_{0A+} = \lambda_b$	$\lambda_{1B+} = \lambda_b \rho \theta$ $\lambda_{1A+} = \lambda_b \theta$

If switching did not occur then the counterfactual hazard would have been

$$\lambda^*(t \mid R,Z) = \lambda_b \theta^R \rho^Z . \quad (2)$$

This differs from equation (2) only for the control switchers (R=0, Z=1): they would not have switched.

3. AGGREGATE DATA

The notation for the data is introduced in this section. The observed aggregate events and times are indexed by the labels in Table **2**. The times and events are aggregated within five observable groups: those in control or treatment ante-switch (0- and 1- respectively), those post-switch in treatment (1+), or post-switch compliers (0A+) or always-takers (0B+) in control. Then we let D_k denote the number of events, T_k the total time at risk and N_k the total number of individual at risk at the start of a given group k=0-, 1-, 1+, 0A+, 0B+. For simplicity, we assume that the number of individuals at risk in both arms at the start of the trial is N , *i.e.* the randomisation ratio is one.

Table 2: Observed Aggregate Number of Events, Survival Times and Number at Risk

R=0	R=1
(D_{0-}, T_{0-})	(D_{1-}, T_{1-})
↓	
R=0	**R=1**
$(D_{0A+}, T_{0A+}, N_{0A+})$ $(D_{0B+}, T_{0B+}, N_{0B+})$	(D_{1+}, T_{1+}, N_{1+})

4. INTENTION TO TREAT (ITT) AND PER-PROTOCOL (PP) ESTIMATORS

Before considering the new estimators, some common approaches are reviewed. The intention-to-treat (ITT) estimator

$$\hat{\theta}_{ITT} = \left(\frac{D_{1-} + D_{1A+} + D_{1B+}}{T_{1-} + T_{1A+} + T_{1B+}} \right) \Big/ \left(\frac{D_{0-} + D_{0A+} + D_{0B+}}{T_{0-} + T_{0A+} + T_{0B+}} \right)$$

estimates the effect of the initial randomisation as opposed to treatment efficacy, because it compares the risk of everyone in treatment to the risk of everyone control, including the always-takers who were given treatment after switching.

Even though ITT estimator is consistent for testing θ = 1, it is a conservative estimate of θ under the switching model. In contrast, the per-protocol (PP) estimator only considers individuals whilst they follow randomisation, censoring switchers at the time of switching:

$$\hat{\theta}_{PP} = \left(\frac{D_{1-} + D_{1A+} + D_{1B+}}{T_{1-} + T_{1A+} + T_{1B+}} \right) \Big/ \left(\frac{D_{0-} + D_{0A+}}{T_{0-} + T_{0A+}} \right)$$

The PP estimator is inconsistent for θ under the switching model, even when θ = 1, and the level of asymptotic bias is linked to the proportion of switchers.

5. SOME ESTIMATORS OF THE COMPLIER AVERAGE CAUSAL EFFECT (CACE)

Estimators of the CACE are next introduced. The switching model is motivated by the CACE

$$\theta_{CACE} = \lambda(t \mid R = 1, Z = 0) / \lambda(t \mid R = 0, Z = 0)$$

as being constant, *i.e.*, under the proposed switching model, we have $\theta_{CACE} = \theta$.

Remark

Although the proposed exponential switching model contains always-takers and compliers prior to switching, it is useful to consider an approximate switching model where only compliers are present prior to switching, *i.e.*,

$$t < t_s : \lambda(t \mid R, Z) = \lambda_b \theta^R$$

$$t > t_s : \lambda(t \mid R, Z) = \lambda_b \theta^{R+(1-R)Z} \rho^Z .$$

In the following section, we will refer to the approximate switching model in discussing the theoretical motivation and consistency of the proposed CACE estimators. This approximation is valid when the number of ante-switch events is small.

CACE Estimation

We first propose an amongst-complier (AC) estimator of the CACE by pooling the ante-switching events and times and post-switching events and times amongst the compliers:

$$\hat{\theta}_{AC} = \left(\frac{D_{1-} + \hat{D}_{1A+}}{T_{1-} + \hat{T}_{1A+}} \right) \Big/ \left(\frac{D_{0-} + D_{0A+}}{T_{0-} + T_{0A+}} \right) \tag{3.10}$$

where:

$$\hat{D}_{1A+} = D_{1+} - D_{0B+} \hat{\alpha} N_{1+} / N_{0B+}$$

$$\hat{T}_{1A+} = T_{1+} - T_{0B+} \hat{\alpha} N_{1+} / N_{0B+} .$$

The proportion who switch α in the treatment arm is estimated by the observed proportion of switching in the control arm

$$\hat{\alpha} = N_{0B+} / (N_{0B+} + N_{0A+}) .$$

The idea is to subtract out the unobserved always-takers from the treatment arm and compare it to the observed compliers in the control arm. In combining the ante-switch effect and post-switch amongst complier effect, $\hat{\theta}_{AC}$ is consistent for the CACE under the approximate switching model.

On the other hand, it is also useful to consider the maximum likelihood estimator under the approximate switching model (for the ante-switch stratum and post-switch compliers stratum) which is the solution to [17]:

$$\theta = \frac{D_{1-} \gamma_-(\theta) + D_{1A+} \gamma_{A+}(\theta)}{D_{0-} \{1 - \gamma_-(\theta)\} + D_{0A+} \{1 - \gamma_{A+}(\theta)\}}$$

$$\gamma_-(\theta) = \frac{T_{0-}}{T_{0-} + T_{1-}\theta}$$

$$\gamma_{A+}(\theta) = \frac{T_{0A+}}{T_{0A+} + T_{1A+}\theta} .$$

Note that in the present case we need estimates of the unobserved data in 1A+. Instead of solving for the MLE iteratively, asymptotic efficiency under the approximate switching model can be obtained by considering a one-step or two-step estimator using the above relation [17]. For example, the Rothman-Boice (RB) estimator amongst compliers, $\hat{\theta}_{AC,RB}$ is the one-step solution with plug-in θ = 1 (on the right-hand-side):

$$\hat{\theta}_{AC,RB} = \frac{D_{1-} \gamma_-(1) + D_{1A+} \gamma_{A+}(1)}{D_{0-} \{1 - \gamma_-(1)\} + D_{0A+} \{1 - \gamma_{A+}(1)\}} ,$$

$\hat{\theta}_{AC,RB}$ can also be interpreted as a weighted extension of $\hat{\theta}_{AC}$ (weighting the ante-switch and post-switch contributions to the overall estimator).

$\hat{\theta}_{AC}$ and $\hat{\theta}_{AC,RB}$ are consistent for the CACE under the approximate switching model, but are not consistent for CACE under the exponential switching model as the ante-switch survival is a mixture of two exponentials in each arm. However we will see in the examples later on that their limits are quite close to the CACE.

Remark

The proposed CACE estimators assume that the number of always-takers in both arms at time of switch is identical. This is justified when the number of ante-switch events is small.

6. ESTIMATING THE COUNTERFACTUAL ITT EFFECT

Let us consider the ITT effect if switching had not occurred, *i.e.*, the rate ratio with counterfactual events and times in the control switchers:

$$\hat{\theta}^*_{ITT} = \frac{D_1 / T_1}{D_0^* / T_0^*} = \frac{D_1 / T_1}{(D_{0-} + D_{0A+} + D^*_{0B+}) / (T_{0-} + T_{0A+} + T^*_{0B+})}.$$

We define the counterfactual ITT effect to be the limit of this counterfactual ITT rate ratio as sample size gets large for a fixed follow-up period under the switching model. Therefore by using consistent estimators of counterfactual events D_0^* and times T_0^* for control switchers, we can consistently estimate the counterfactual ITT effect.

A Time and Event Adjusted Estimator for the Counterfactual ITT Effect

We now propose a time and events adjusted method for estimating the counterfactual ITT effect. Let K = $\alpha N S_{0-}(t_s)$ denote the expected number of always-takers at risk in the control arm at the time of switch t_s, where $S_{0-}(t_s)$ is the probability of a control patient surviving till switching. Then the expectation of the observed and counterfactual number of events $E(D_{0B+})$ and $E(D^*_{0B+})$ can be expressed as:

$$E(D_{0B+}) = K\{1 - S_{0B}(t_e \mid T > t_s)\}$$
$$E(D^*_{0B+}) = K\{1 - S^*_{0B}(t_e \mid T > t_s)\}$$

where $S_{0B}(t_e \mid T > t_s)$ is the conditional probability of a control switcher being alive at t_e given they were alive at t_s. The counterfactual survival probability is $S^*_{0B}(t_e \mid T > t_s) = S_{0B}(t_e \mid T > t_s)^{1/\theta}$ under the switching model. This gives the relation

$$E(D^*_{0B+}) = E(D_{0B+})w$$

where

$$w = \frac{\{1 - S^*_{0B}(t_e \mid T > t_s)\}}{\{1 - S_{0B}(t_e \mid T > t_s)\}}.$$

Similarly, the relation between the observed and counterfactual total event times of control switchers is

$$E(T^*_{0B+}) = \theta E(T_{0B+})w$$

Using these relations, the proposed estimator of the counterfactual ITT effect can be written as:

$$\hat{\theta}^*_{ITT} = \frac{D_1 / T_1}{(D_{0-} + D_{0A+} + D^*_{0B+}) / (T_{0-} + T_{0A+} + T^*_{0B+})}$$

where

$$T^*_{0B+} = \theta T_{0B+} w$$
$$D^*_{0B+} = D_{0B+} w.$$

$\hat{\theta}^*_{ITT}$ is consistent for the counterfactual effect under the switching model given θ or a consistent estimator of θ. In practice, θ might be substituted by the ante-switch rate ratio and $S_{0B}(t_e \mid T > t_s)$ is estimated from the observed survival probability among the control always-takers.

In the limit of light censoring and heavy censoring, the counterfactual ITT estimator reduces respectively to time-adjustment only and event-adjustment only.

7. SIMULATION EXAMPLES

In the following examples, the survival times are simulated according to the proposed switching model. We simulated 10000 replicates of sample size N = 3000 (in each arm) of exponential survival times with parameters switching time t_s = 0.1, switching proportion at the start of trial α =0.6, baseline hazard of one and always-taker effect ρ = 0.5.

We look at six scenarios, summarised in Table **3**. The first three have beneficial treatment effects θ =0.5 and the last three have detrimental treatment effects θ =1.5. Each set is composed of light censoring, mid-censoring and heavy censoring. Furthermore, we test the estimators for early switching t_s = 0.1 and late switching t_s = 0.5. As the switching time increases, the

difference in switching proportions at t_s becomes more pronounced. For t_s = 0.1, the switching proportions for control and treatment at t_s are: (57%, 59%) for θ = 0.5 and (57%, 56%) for θ = 1.5. For t_s = 0.5, the two switching proportions are (47%, 53%) for θ = 0.5 and (41%, 47%) for θ = 1.5. The counterfactual ITT effect (θ^*_{ITT}) is obtained using one simulation of counterfactuals of sample size ten millions.

Table 3: Six Scenarios

Scenario	θ	t_e
1	0.5	t_s +0.1 (light cens)
2	0.5	t_s +1 (mid cens)
3	0.5	t_s +5 (heavy cens)
4	1.5	t_s +0.1 (light cens)
5	1.5	t_s +1 (mid cens)
6	1.5	t_s +5 (heavy cens)

Table **4** and **5** summarises the results for t_s = 0.1 and t_s = 0.5 respectively, where mean squared error (MSE) with respect to the CACE and the counterfactual ITT effect are given in brackets. For t_s = 0.1, the ITT estimator is conservative for both effects whilst the PP estimator is anti-conservative under beneficial treatment effects and conservative under detrimental treatment effects. The Rothman-Boice type estimate $\hat{\theta}_{AC,RB}$ is closer in mean to the true CACE than $\hat{\theta}_{AC}$, but it is less efficient for θ = 1.5. In general, $\hat{\theta}^*_{ITT}$ is the closest to the CACE and the counterfactual ITT effect for both beneficial and detrimental treatment effects.

Similar results are observed when the switching time is increased to t_s = 0.5. Whilst all estimators are more accurate for this later switching time, $\hat{\theta}^*_{ITT}$ still gives the best estimates of both the CACE and the counterfactual ITT effect overall.

For both switching times, both CACE estimators and the counterfactual ITT estimator give far closer estimates of the two effects than the ITT and PP estimators.

8. DISCUSSION

We presented simple estimators for the control-to-treatment mid-trial switching problem. Modeling

Table 4: Simulated Example with t_s =0.1, MSE w.r.t θ and θ^*_{ITT} are Given in Brackets

	Scenario 1 (light cens)	Scenario 2 (mid cens)	Scenario 3 (heavy cens)
θ	0.500	0.500	0.500
θ^*_{ITT}	0.502	0.510	0.514
$\hat{\theta}_{ITT}$	0.566 (0.679, 0.654)	0.674 (3.101, 2.771)	0.812 (9.781, 8.949)
$\hat{\theta}_{PP}$	0.450 (0.412, 0.431)	0.377 (1.553, 1.805)	0.347 (2.355, 2.792)
$\hat{\theta}_{AC}$	0.506 (0.338, 0.336)	0.512 (0.182, 0.167)	0.521 (0.225, 0.185)
$\hat{\theta}_{AC,RB}$	0.504 (0.335, 0.334)	0.504 (0.166, 0.167)	0.507 (0.176, 0.175)
$\hat{\theta}^*_{ITT}$	0.505 (0.306, 0.304)	0.511 (0.184, 0.173)	0.516 (0.251, 0.226)
	Scenario 4 (light cens)	**Scenario 5 (mid cens)**	**Scenario 6 (heavy cens)**
θ	1.500	1.500	1.500
θ^*_{ITT}	1.492	1.477	1.489
$\hat{\theta}_{ITT}$	1.352 (2.92, 2.697)	1.210 (8.584, 7.303)	1.147 (12.586, 11.809)
$\hat{\theta}_{PP}$	1.340 (3.459, 3.216)	1.092 (16.848, 15.026)	1.006 (24.558, 23.466)
$\hat{\theta}_{AC}$	1.494 (1.482, 1.479)	1.469 (1.028, 0.940)	1.456 (1.756, 1.669)
$\hat{\theta}_{AC,RB}$	1.499 (1.524, 1.529)	1.493 (1.104, 1.126)	1.495 (2.115, 2.117)
$\hat{\theta}^*_{ITT}$	1.499 (1.428, 1.433)	1.479 (0.924, 0.879)	1.492 (1.213, 1.207)

Table 5: Simulated Example with t_s =0.5, MSE w.r.t θ and θ^*_{ITT} are Given in Brackets

	Scenario 1 (light cens)	Scenario 2 (mid cens)	Scenario 3 (heavy cens)
θ	0.500	0.500	0.500
θ^*_{ITT}	0.505	0.512	0.513
$\hat{\theta}_{ITT}$	0.524 (0.136, 0.115)	0.616 (1.396, 1.138)	0.748 (6.218, 5.586)
$\hat{\theta}_{PP}$	0.492 (0.075, 0.085)	0.442 (0.367, 0.517)	0.405 (0.920, 1.185)
$\hat{\theta}_{AC}$	0.508 (0.092, 0.086)	0.526 (0.160, 0.112)	0.558 (0.478, 0.344)
$\hat{\theta}_{AC.RB}$	0.506 (0.089, 0.085)	0.513 (0.104, 0.088)	0.523 (0.182, 0.141)
$\hat{\theta}^*_{ITT}$	0.506 (0.087, 0.084)	0.514 (0.091, 0.073)	0.517 (0.100, 0.074)
	Scenario 4 (light cens)	**Scenario 5 (mid cens)**	**Scenario 6 (heavy cens)**
θ	1.500	1.500	1.500
θ^*_{ITT}	1.483	1.474	1.489
$\hat{\theta}_{ITT}$	1.438 (0.729, 0.546)	1.285 (4.767, 3.708)	1.212 (8.404, 7.804)
$\hat{\theta}_{PP}$	1.447 (0.653, 0.500)	1.273 (5.323, 4.202)	1.176 (10.634, 9.957)
$\hat{\theta}_{AC}$	1.482 (0.448, 0.416)	1.440 (0.746, 0.500)	1.406 (1.380, 1.191)
$\hat{\theta}_{AC.RB}$	1.485 (0.447, 0.425)	1.468 (0.604, 0.504)	1.458 (1.099, 1.021)
$\hat{\theta}^*_{ITT}$	1.486 (0.444, 0.424)	1.471 (0.473, 0.388)	1.485 (0.484, 0.464)

survival times as exponentially distributed conditional on principal compliance, we combined ante-switch and post-switch treatment compliers times and events to give several estimators of the CACE effect that are consistent under an approximate model using aggregate data. We also discussed estimating the counterfactual ITT effect which involves recovering the events and times had no switching occurred. Using simulations, we showed that the CACE estimators and the counterfactual ITT estimator can offer significant improvements over the conventional approaches in estimating both effects in our setup. The estimators can be easily extended for the piecewise exponential case.

When individualised data is available for randomised trials with switching, more complicated models such as the Cox model can be considered. One might extend the CACE estimators of Cuzick and others (2007) and Loeys and Goetghebeur (2003), but assumptions need to made regarding the survival of the unobserved compliers and switching proportion in the treatment arm. Parametric models can be used for specifying how the unobserved complier switching proportion in the treatment arm varies with time but the necessary inference is certainly not straightforward. A fuller discussion of such extensions for the Cox model will follow in future work.

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