ADEMP-PreReg
Simulation study of deprescribing in a target-trial emulation

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Template based on the paper:
Siepe, B. S., Bartoš, F., Morris, T. P., Boulesteix, A.-L., Heck, D. W., & Pawel, S. (2024). Simulation Studies for Methodological Research in Psychology: A Standardized Template for Planning, Preregistration, and Reporting. *Psychological Methods*. https://doi.org/10.1037/met0000695, https://doi.org/10.31234/osf.io/ufgy6

General Information

This template can be used to plan and/or preregister Monte Carlo simulation studies according to the ADEMP framework [1]. The publication associated with this template is [2]. Alternative Google Docs and Word versions of this template are available at (https://github.com/bsiepe/ADEMP-PreReg). To time-stamp your protocol, we recommend uploading it to the Open Science Framework (https://osf.io/) or Zenodo (https://zenodo.org/). When using this template, please cite the associated article [2]. If you have any questions or suggestions for improving the template, please contact us via the ways described at (https://github.com/bsiepe/ADEMP-PreReg). For LaTeX users of this template, we provide simple commands to exclude the instructions, explanations, and example boxes from their compiled document.

Using this template

Please provide detailed answers to each of the questions. If you plan to perform multiple simulation studies within the same project, you can either register them separately or number your answers to each question with an indicator for each study. As the planning and execution of simulation studies often involves considerable complexity and unknowns, it may be difficult to answer all the questions in this template or some changes may be made along the analysis pathway. This is to be expected and should not deter from preregistering a simulation study; rather, any modifications to the protocol should simply be reported transparently along with a justification, which will ultimately add credibility to your research. Finally, the template can also be used as a blueprint for the reporting of non-preregistered simulation studies.

1 General Information

1.1 What is the title of the project?

Evaluating methods to quantify the effect of deprescribing a medication on patient clinical outcomes using a simulation study.

1.2 Who are the current and future project contributors?

Ryan Muddiman, Fiona Boland, Emma Wallace, Tom Fahey, Teresa Perez, Florencia Ines Aiello Battan, Li Wei, Mary Walsh, Frank Moriarty.

1.3 Provide a description of the project.

We will investigate the performance of several estimation methods in quantifying the effects of deprescribing a medication (the intervention) on a population. The simulation is aimed at informing the design and analysis of observational studies which emulate a hypothetical randomised control trial (RCT), or target trial, to examine the effect of deprescribing. Causal estimation of the effects of deprescribing using observational data poses several potential challenges[3], such as time-varying confounding and measurement

error. These may lead to biases when overlooked and affect conclusions. In the target trial we propose a study design using the following framework. The population of interest is patients who have been regularly prescribed a specific medication. The intervention will be the immediate stopping of taking the medication. The comparison will be the continued use of the medication. The outcomes of interest will be the occurrence of adverse events or death. A simulation will be developed to generate a large artificial patient observation dataset that closely mimics patient health records. The dataset will include variables necessary to analyse deprescribing in realistic scenarios, such as patient characteristics and event histories. Prespecified risks related to the intervention will be simulated and then estimated using standard methods commonly used in pharmacoepidemiology, such as time-to-event analysis.

1.4 Did any of the contributors already conduct related simulation studies on this specific question?

We did not conduct previous simulation studies in this area.

2 Aims

2.1 What is the aim of the simulation study?

The aim of this study is to test multiple estimation methods in terms of their accuracy. The primary estimand is the "effect of deprescribing on outcomes", where outcomes are adverse events or death. The simulated dataset will be constructed by defining the ground truth longitudinal data and then applying realistic censoring mechanisms to reflect how data is captured in real-world settings. The final dataset for analysis should then represent the relevant data recorded in an electronic health record (EHR). The true effect will be estimated using time-to-event analysis. We will analyse the data using a target trial emulation framework. Potential approaches to estimating the causal effect include:

- Cox proportional hazards model
- Extended Cox model
- Joint models

3 Data-Generating Mechanism

3.1 How will the parameters for the data-generating mechanism (DGM) be specified?

We aim to simulate the causal dependence structure as accurately as possible in order to test different analytic methods. The dependence structure of an intervention such as deprescribing can be represented with a directed acyclic graph[3], such as the one shown in Figure 1.

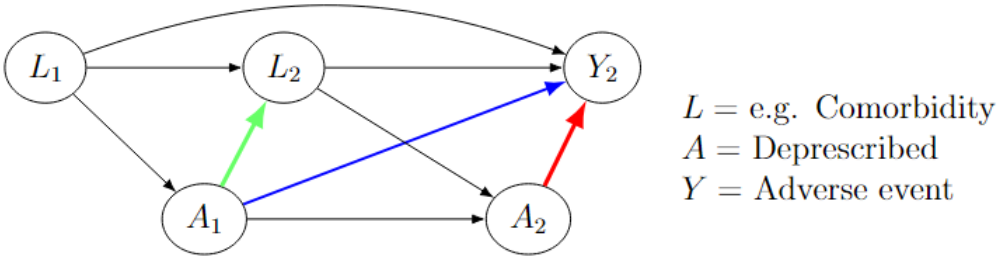

Figure 1: Causal directed acyclic graph of dependence structure for deprescribing at two distinct times. L is a measured covariate, A is the intervention and Y is an outcome of interest. The red path describes the the causal effect of deprescribing on patient outcomes. The blue path describes how the prior treatment may also affect the outcome. The green path describes the direct effect of treatment on a covariate (mediator), inducing treatment-confounder feedback. For clarity, the graph does not show unmeasured confounding.

Data will be generated assuming all patients are independent. Each patient will have baseline covariates drawn from a multivariate distribution that is specified at the outset. The marginal distributions will be specified exactly, and we will generate the covariance-variance matrix of the joint distribution using specified values for each entry, and the Generate, Sort, and Correlate (GSC[4]) algorithm to test the validity of the covariance-variance matrix.

The baseline covariates will be used to calculate the initial generator matrix $\alpha(t)$ of a five-state continuous-time multi-state model (CTMM). The states of the model will be

$$V = \{\text{Prescribed}, \text{Adverse event-minor}, \text{Adverse event-major}, \text{Deprescribed}, \text{Dead}\}$$

Each patient will then have a simulated trajectory over V using the time-dependent generator. The time-dependence of $\alpha(t)$ will be simulated using a baseline hazard rate where the time corresponds to time since entering the deprescribed state. The baseline hazard rates will therefore be time non-homogenous (semi-Markov). The hazard rates will be modified by multiplicative time-varying effects and/or covariates. The structure of the CTMM has been determined using assumptions about the likely dependence between observable biological events. Figure 2 is the state diagram representing the possible transitions of the stochastic data-generating process.

The initial state of all patients will be $V = 1$. $V = 5$ will be an absorbing state from which no transitions can occur. Variables of interest for individual patients will be the history of occupied states $\mathcal{H}$ and the time spent in each state τ (the holding time). These values will form the event history of each person. From these quantities, a survival analysis will be performed on simulated populations of patients. The population size for each simulation run will be denoted n_{obs} and the number of simulation runs will be denoted n_{sim}. We give the values of these parameters in Table 5.

The CTMM can be specified by a baseline generator matrix $\alpha^0(t)$ (all covariates equal to zero), the multiplicative effect of covariates and the covariates themselves. The baseline

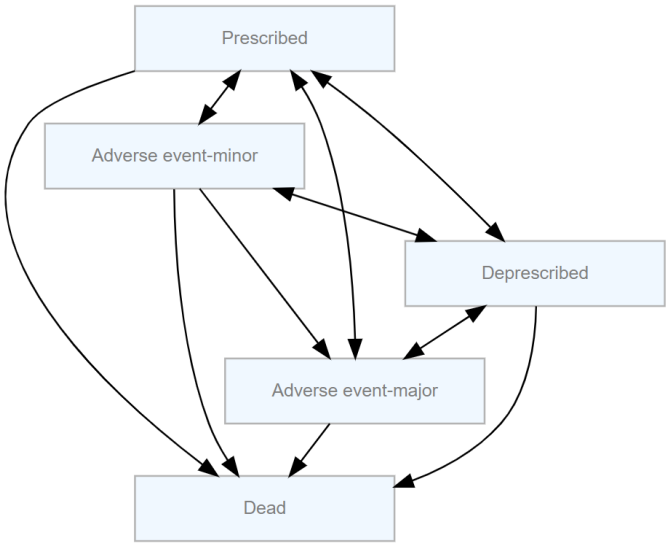

Figure 2: State diagram for the simulation. All simulations begin in the prescribed state.

generator matrix is defined here as the 5×5 matrix

$$\alpha^0(t) = \begin{bmatrix} 0 & \alpha^0_{12} & \alpha^0_{13} & \alpha^0_{14} & \alpha^0_{15} \\ \alpha^0_{21} & 0 & \alpha^0_{23} & \alpha^0_{24} & \alpha^0_{25} \\ \alpha^0_{31} & 0 & 0 & \alpha^0_{34} & \alpha^0_{35} \\ \alpha^0_{41} & \alpha^0_{42} & \alpha^0_{43} & 0 & \alpha^0_{45} \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{matrix} \text{Prescribed} \\ \text{Adverse event-minor} \\ \text{Adverse event-major} \\ \text{Deprescribed} \\ \text{Dead} \end{matrix} \tag{1}$$

where entry $\alpha^0_{ij}(t)$ is the baseline transition hazard from state i to state j at time t. The diagonal entries in α^0 are zero, representing the lack of self-transitions. The all-cause hazard out of state i is $\alpha_i \triangleq \sum_j \alpha_{i,j}$. Baseline cause-specific hazards are defined as either Weibull or Gompertz distributions. The Weibull hazard rate will be parametrised as

$$\alpha^0_{i,j}(t) = \theta k t^{k-1} \tag{2}$$

where $\theta, k \in \mathbb{R}^+$ are the scale and shape parameter of the Weibull distribution. The Gompertz hazard rate is given by

$$\alpha^0_{i,j}(t) = a \cdot e^{b \cdot Age} \tag{3}$$

Where a, b and Age are the Gompertz scale and shape parameters and patient age, respectively. We give the specific values of the parameters of all baseline hazards in Table 1 and plots of the hazard rates for time-varying hazards in Figure 3. The mortality hazard will use the Gompertz distribution with values obtained from Eurostat life tables.[5] The cause-specific hazard from state i to state j is thus expressed as

$$\alpha_{i,j}(t) = \alpha^0_{i,j}(t) \cdot \exp[\mathbf{z}^T(t)(\boldsymbol{\beta} + \boldsymbol{\gamma} f(t))] \tag{4}$$

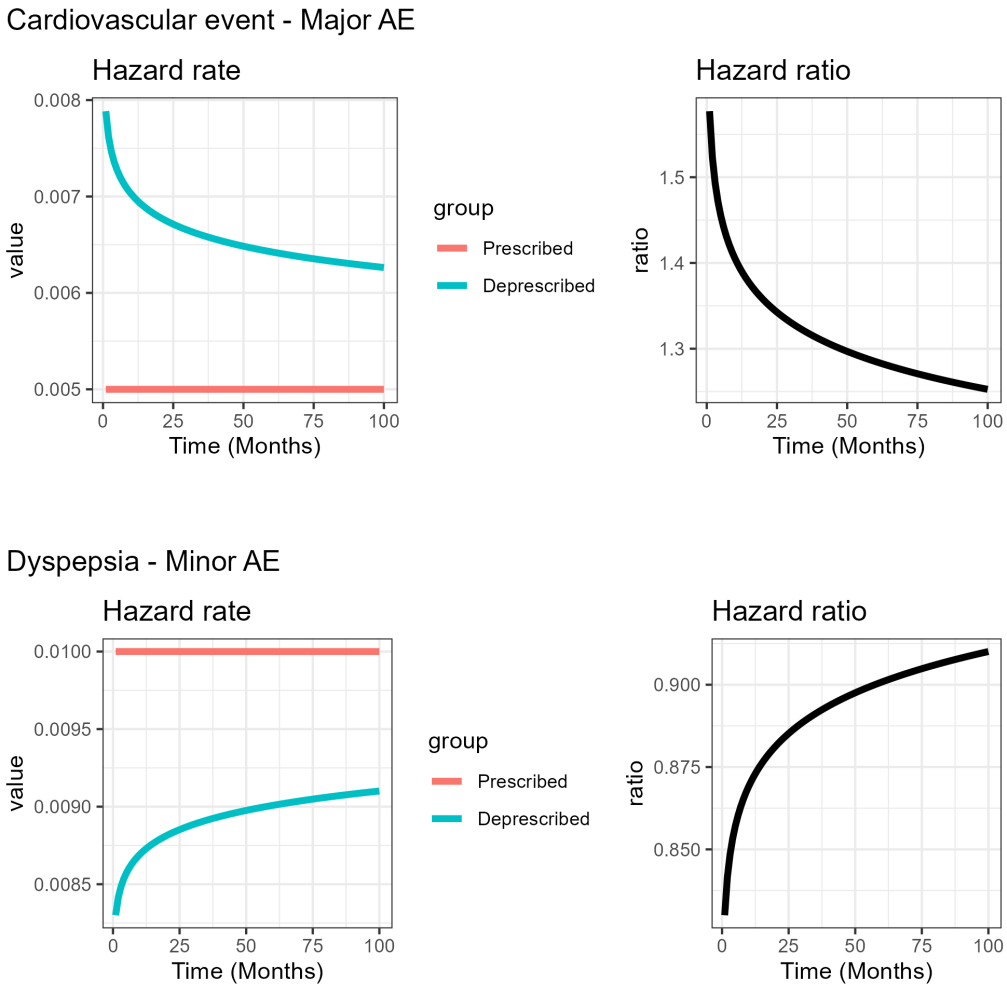

Figure 3: Time-varying hazard rates and hazard ratio of intervention for the two adverse events.

with $\beta, \gamma, z \in \mathbb{R}$ being the constant effect magnitude, time-dependent effect magnitude and covariates respectively. $f(t)$ is a time transformation function defined as one of three deterministic functions

$$f(t) \triangleq \begin{cases} t \\ t^2 \\ \log(t) \end{cases} \tag{5}$$

The stochastic process given by the baseline generator matrix will not in-general assume the Markov property, since it is a renewal process with time-varying intensities. This precludes the use of the Kolmogorov-Chapman equations for solving for marginal process features such as the steady-state occupancy probability. Furthermore, intensities will condition on past process history resulting in adapted processes.

Further to the instantaneous hazard rates, we will simulate clinically plausible causal

Table 1: Parameter values of baseline hazard rates.

Transition	**Distribution**	**a (months^{-1})**	**b (months^{-1})**	**Shape (-)**	**Scale (months^{-1})**	**Source**
Prescribed to AE-major	Weibull	-	-	1.00	5.00×10^{-3}	CJ[a]
Prescribed to AE-minor	Weibull	-	-	1.00	1.00×10^{-2}	CJ
Prescribed to dead	Gompertz	3.28×10^{-5}	7.53×10^{-3}	-	-	LT[b]
Prescribed to deprescribed	Weibull	-	-	1.00	2.96×10^{-3}	RWE[c]
Deprescribed to prescribed	Weibull	-	-	1.00	1.00×10^{-3}	CJ
Deprescribed to dead	Gompertz	3.28×10^{-5}	7.53×10^{-3}	-	-	LT
Deprescribed to AE-minor	Weibull	-	-	1.02	8.30×10^{-3}	CJ
Deprescribed to AE-major	Weibull	-	-	9.50×10^{-1}	8.30×10^{-3}	CJ
AE-minor to prescribed	Weibull	-	-	1.00	5.00×10^{-4}	CJ
AE-minor to AE-major	Weibull	-	-	1.00	1.00×10^{-2}	CJ
AE-minor to deprescribed	Weibull	-	-	1.00	5.92×10^{-3}	CJ
AE-minor to dead	Gompertz	3.28×10^{-5}	7.53×10^{-3}	-	-	LT
AE-major to prescribed	Weibull	-	-	1.00	1.00×10^{-4}	CJ
AE-major to deprescribed	Weibull	-	-	1.00	2.96×10^{-2}	CJ
AE-major to dead	Gompertz	3.28×10^{-5}	7.53×10^{-3}	-	-	LT

[a]CJ: Clinical judgement
[b]LT: EUROSTAT lifetables[5]
[c]RWE: Real world evidence[6]

structure for each patient as follows. We first describe a hypothetical clinical question and then give the assumed causal structure.

Clinical example – low-dose aspirin

Considering the population, intervention, comparison and outcome (PICO); among people who have been regularly prescribed low-dose aspirin for at least two years, what is the effect of deprescribing the aspirin (immediate stopping) compared to continuation on the following outcomes: dyspepsia (AE-minor, increased by aspirin), major gastrointestinal bleed (AE-major, increased by aspirin), cardiovascular events (AE-major, reduce by aspirin), death? The covariates we aim to simulate in this study are given in Table 2. We specify a covariate that is dependent on the stochastic process as an internal covariate, and one that does not as an external covariate.[7] Time-dependent external covariates may have their history specified prior to the stochastic simulation, whereas internal covariates are generated by the simulation itself.

X_1 will be a linear function of time with slope 1 and intercept equal to the baseline value as described in Table 3. X_2 will be a latched indicator function with value 1 when the state 4 is entered, resetting to zero if state 1 is entered. X_3 will be defined as the number of previous major adverse events $N_{\text{adverse-events}}$, which may be used as a marker for deprescribing, can be influenced by deprescribing, and is associated with the clinical outcomes. X_4 will be a linear function of time with slope and intercept equal to the baseline value in Table 2. X_5 will be a binary random variable and X_6 will be an indicator

Table 2: Covariates and their roles, data types, time-dependency, sources, and examples.

Covariate	**Role**	**Data type**	**Time-dependent**	**Source**	**Example**
X_1	Baseline confounder	Continuous	Yes	External	Age
X_2	Time-varying exposure	Binary	Yes	Internal	Deprescribed
X_3	Time-varying mediator	Ordinal	Yes	Internal	$N_{\text{adverse-events}}$
X_4	Tim-varying confounder	Continuous	Yes	External	Comorbidity
X_5	Effect modifier	Binary	No	External	Sex
X_6	Indicator of deprescribing	Binary	Yes	Internal	Ever deprescribed

Table 3: Distributions and parameters for non-zero baseline covariates.

Covariate	**Distribution**	**Parameters**
X_1	Gaussian	Mean $\mu = 50$, standard deviation $\sigma = 10$
X_4	Gaussian	Mean $\mu = 0$, standard deviation $\sigma = 1$
X_5	Bernoulli	Probability male $p = 0.5$

function with value 1 when state 4 is entered and thereafter. Given the state-space, we assume full adherence to the medication in these studies such that being in the prescribed state means the patient is prescribed and following the given dose. The time zero of the simulation will correspond to a period of at least 6 months after the patients have been prescribed a medication for continued use. The covariates X_2, X_3 and X_6 will be generated as internal adapted processes, with an initial value of zero for all patients.
The baseline distribution $\mathbf{X_b} \triangleq (X_1, X_4, X_5)^T$ will be generated from a multivariate distribution with marginal moments as per Table 3. The target correlation matrix will be specified as

$$\text{Corr}(\mathbf{X_b}) = \begin{bmatrix} 1 & 0.2 & 0.2 \\ 0.2 & 1 & 0.2 \\ 0.2 & 0.2 & 1 \end{bmatrix} \tag{6}$$

The effects of covariates on the transition hazards are shown in Table 4.

Simulation pseudocode

- Patients all begin prescribed (i.e., regularly prescribed aspirin for at least two years).
- The hazard of the aspirin being deprescribed depends on age (X_1), comorbidity

Table 4: Covariate effects (log-hazard ratio)

Transition	X_1	X_2	X_3	X_4	X_5	X_6
Prescribed to AE-major	0.00	0.00	0.00	0.00	0.00	0.00
Prescribed to AE-minor	0.00	0.00	0.00	0.00	0.00	0.00
Prescribed to dead	0.00	0.00	0.00	0.00	0.00	0.00
Prescribed to deprescribed	0.01	1.00	0.00	1.00	-1.00	0.00
Deprescribed to prescribed	0.00	0.00	0.00	0.00	0.00	0.00
Deprescribed to dead	0.00	0.00	0.00	0.00	0.00	0.00
Deprescribed to AE-minor	0.00	0.00	0.00	0.00	0.00	0.00
Deprescribed to AE-major	0.00	1.00	1.00	1.00	0.00	0.00
AE-minor to prescribed	0.00	0.00	0.00	0.00	0.00	0.00
AE-minor to AE-major	0.00	0.00	0.00	0.00	0.00	0.00
AE-minor to deprescribed	0.00	0.00	0.00	0.00	0.00	0.00
AE-minor to dead	0.00	0.00	0.00	0.00	0.00	0.00
AE-major to prescribed	0.00	0.00	0.00	0.00	0.00	0.00
AE-major to deprescribed	0.00	0.00	0.00	0.00	0.00	0.00
AE-major to dead	0.00	0.00	0.00	0.00	0.00	0.00

status (X_4) and past deprescribing history (X_6, i.e., any previous episodes of deprescribing).

- When someone is deprescribed, their future risk (or probability) of ever being deprescribed again is reduced (our simulation scenario focuses on deprescribing of one type of medication, so we assume that once a simulated patient is deprescribed, the probability of them being deprescribed again in the future is lower).

- Deprescribing has an initial increased risk of cardiovascular events, which after some time reduces to a lower but still elevated level versus the continuation group.

- The hazard of being deprescribed for those that are continuing (i.e., prescribed) depends on whether an adverse event has occurred (e.g., the occurrence of dyspepsia doubles the deprescribing risk, and gastro-intestinal bleeds cause a 10-fold increase in deprescribing risk).

- The hazard of being prescribed for those that are deprescribed (i.e., re-prescribing) depends on whether an adverse event has occurred, whether the event is related to the medication or the disease the medication is treating, and the severity (X_3, e.g., the occurrence of dyspepsia halves the re-prescribing risk, and gastro-intestinal bleeds cause a 10-fold decrease in re-prescribing risk).

We will then apply to the above event history data a censoring mechanism as follows. Data will be administratively censored using a specified end of follow-up time. We also aim to simulate informative censoring using random sampling of the censoring time with modification of the censoring hazard by patients' covariates. Informative censoring will depend on the exposure.

3.2 What will be the different factors of the data-generating mechanism?

We will vary the following factors for data generation:

- Parameters of the baseline hazard rates (θ,k) of transitions between states.

Instead of focusing our simulation on one scenario, we will present results for multiple scenarios (using variations on the base-case in Table 1), that should cover a broad range of drug classes.

3.3 If possible, provide specific factor values for the DGM as well as additional simulation settings.

The main factors will be the magnitude of the cause-specific hazard ratio for deprescribed versus prescribed states and the size of the full population. For the hazard ratio, we will vary the base-case values of the ratio of the scale parameters by (-10%, -20% -50%). The population sample size will be varied by (-20%, -50%).

3.4 If there is more than one factor: How will the factor levels be combined and how many simulation conditions will this create?

Factors will be combined in a fully-factorial fashion resulting in 4 (hazard ratios) by 3 (populations), or 12 total results per method.

4 Estimands and Targets

4.1 What will be the estimands and/or targets of the simulation study?

Our primary estimand is the hazard ratio of intervention (deprescribing) versus no intervention (continuing the medication) with respect to adverse events and death. The intervention, deprescribing, is immediate stopping of the medication. This will be identified in observational databases based on a cessation of a prescription. Non-adherence while prescribed is a confounder that is rarely measured in reality, and therefore it is also not reflected in the DGM. The estimand of interest is a population average treatment effect (ATE). Since the simulation is based on conditional cause-specific hazards, the true causal marginal ATE is not specified explicitly in the simulation parameters. The causal marginal ATE is also not equal to the conditional treatment effect due to non-collapsibility of the hazard ratio. Instead, it will be estimated using g-computation of the uncensored model. When the outcome of interest is a major adverse event, there are possible intercurrent events such as treatment switching (e.g. changing from deprescribed to prescribed) and death. The strategies for addressing these events will follow ICH E9 (R1). Since death is a terminal event, the treatment policy strategy is not applicable. We will identify and estimate two different estimands. The first estimand will

use the intention-to-treat principle and thus ignore non-terminal competing events (treatment discontinuation after baseline), leading to an estimand that targets the effect of being assigned treatment, regardless of actual treatment received. The second estimand will use the hypothetical intervention "the patient does not switch their treatment after assignment". We will obtain the true marginal ATEs according to the following procedure.

Obtaining the ground truth via g-computation

In obtaining the marginal ATE, we will ensure the three requirements for causal identifiability, namely consistency, exchangeability and positivity.[8] Consistency will hold because the simulation is a well-defined representation of (an idealised) reality with one version of the treatment. Exchangeability will be ensured by cloning each patient and simulating their outcomes under two scenarios (treated and untreated). Positivity will hold because everyone will be both treated and untreated using the cloning procedure. Furthermore, independent censoring will hold since we will simulate the counterfactual outcomes using the g-computation approach on the fully uncensored simulation data.

1. Estimand 1: Simulate a cohort where everyone starts in "deprescribed", and another cohort where everyone starts in "prescribed". The ATE can then be estimated from the difference in time to events between the cohorts. The difference can be summarised using a cox model with initial state as the only covariate. The intervention corresponds to assigning the specified treatment at baseline.

2. Estimand 2: Set the hazard of treatment switching to zero by intervening on cause-specific hazards (a hypothetical intervention that is possible). Simulate a cohort starting in "prescribed" and another cohort starting in "deprescribed". The ATE can then be estimated from the difference in time to events between the cohorts. The difference can be summarised using a cox model with initial state as the only covariate.

Estimand 1 will thus ignore the post-baseline treatment status, whereas estimand 2 will prevent treatment switching. In both estimands, death is a competing intercurrent event that prevents the further occurrence of the outcome of interest. Thus, the intercurrent event of death will be addressed using the while on treatment strategy, treating death as a competing event (artificially censor on death), for both estimand 1 and 2.

5 Methods

5.1 How many and which methods will be included and which quantities will be extracted?

We will estimate the relative effect of the intervention versus the comparison groups primarily using time-to first event models (Cox model). Other methods that are suitable for estimating the estimand are marginal recurrent events analysis and intensity-based multi-state/competing risks models. We will assume that in general, the correctly specified inference model (the "true" model) will not be identified in observational scenarios due to the complex nature of observational data. Thus, the parametric models we will

employ for causal inference will always be somewhat mis-specified due to parametric modelling assumptions. We are interested in informing model selection for causal inference in this regard. Two main approaches for model selection are the application of domain knowledge and data-adaptive methods. Since this is a simulation study, application of domain knowledge is redundant, since we are biased from knowing the DGM. Therefore, an obvious choice of candidate models are those that are commonly employed in causal inference studies. Data-adaptive approaches that make less-restrictive assumptions about the DGM (such as the super-learner approach) will also be explored, as these do not require domain knowledge.

6 Performance Measures

6.1 Which performance measures will be used?

From each simulation we will calculate the coverage of the confidence interval specified with respect to the true baseline hazard ratio. The true hazard ratio will be determined from g-computation on the uncensored data. The coverage is then the proportion of times that the true hazard ratio value is within the confidence interval specified by the inference model. We will also report the bias from the true ATE as the difference between the true effect and the estimate. The Monte-Carlo standard error of coverage and bias will also be reported.

6.2 How will Monte Carlo uncertainty of the estimated performance measures be calculated and reported?

Monte Carlo uncertainty will be reported in the form of Monte Carlo Standard Errors (MCSE).

6.3 How many simulation repetitions will be used for each condition?

For each study we will use the following parameters:

Table 5: Static parameters of each simulation.

Parameter	Value
n_{obs}	2000
n_{sim}	400

The number of simulations was based on Burton et al[9]. The minimum number of repetitions required to produce an estimate within 5 % of the true value at 5 % significance level was determined according to the following equation

$$n_{\text{sim}} = \left(\frac{Z_{1-\alpha/2}\,\sigma}{\delta} \right)^2 \tag{7}$$

Where $Z_{1-\alpha/2}$ is the $1-(\alpha/2)$ quantile of the standard normal distribution, σ^2 is the variance of the estimate and δ is the permissible deviation from the true parameter. Both the true value of the estimand and the variance of its estimate are required to be known to determine n_{sim} , however these are not explicitly defined in the simulation parameters. The true value was estimated to be approximately 1 based on the conditional cause-specific hazard ratios and its variance 0.2 based on trial simulations. Thus n_{sim} should be no less than 308. We chose to increase this to 400 as a conservative measure. The number of individual patients, n_{obs} was chosen based on a reasonable value of expected sample size in real analyses. We expect that conclusions about relative performance will remain valid for larger sample sizes, however we will test this hypothesis using a single evaluation of DGM parameters using a value of 10000.

6.4 How will missing values due to non-convergence or other reasons be handled?

We will treat the simulated data and inference separately. Non-convergence during the simulation of data will be handled by determining the root cause and re-simulating until the dataset has no missing values. Non-convergence in the analysis of the data will most likely be due to the lack of samples in strata. This non-convergence will be handled on a case-by-case basis and the analysis ignored in the computation of the performance measures.

6.5 How do you plan on interpreting the performance measures? (optional)

7 Other

7.1 Which statistical software/packages do you plan to use?

All simulation and analysis will be performed in R. There are multiple inference packages in R for analysing survival data: **survival**[10], **mstate**[11] and **muhaz**[12]. At this stage, the choice of software packages has not yet been finalised.

7.2 Which computational environment do you plan to use?

We intend to use R for performing the Monte-Carlo simulations. We will develop custom scripts for the simulation.

7.3 Which other steps will you undertake to make simulation results reproducible? (optional)

We will upload the fully reproducible simulation script to GitHub (https://github.com/moriarty-pharmacoepi/DIAMOND) and a data set containing all relevant estimates, standard errors, and p-values for each repetition of the simulation to OSF (https://osf.io). We will also include the seed used for random number generation in the code.

7.4 Is there anything else you want to preregister? (optional)

We will choose the simulation seed based on the value of the USD-EURO (European Central Bank Euro Foreign Exchange Reference Rates), on 16/06/2025, taking the first 4 digits after the decimal place.

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