

Target Trial Emulation for Comparing Repeated Treatment Schedules: Pitfalls and Key Decisions

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Motivation

- No randomized controlled trial has compared **annual vs biennial screening mammography** head-to-head, in part because of the long follow-up needed to observe clinically meaningful endpoints
- Currently, different organizations give *differing recommendations*:
 - United States Preventive Services Task Force: biennial screening for women over 40
 - American Cancer Society, Society of Breast Imaging: annual screening for women over 40



Figure 1: Visualizing annual vs biennial mammography screening schedules.

US Preventive Services Task Force. JAMA. 2024. doi:10.1001/jama.2024.5534

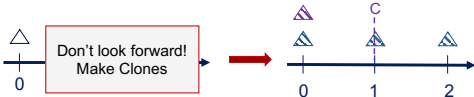
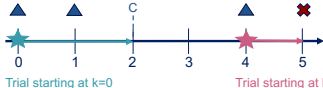
ACS Breast Cancer Screening Guidelines. Accessed August 14, 2024.

Monticciolo DL, et al. Journal of the American College of Radiology. 2021. doi:10.1016/j.jacr.2021.04.021

Overview of Target Trial Emulation

- **Target trial emulation (TTE)** applies the principles of randomized trials to observational studies to avoid suboptimal study design
 - Two-stage approach

Table 1: Obstacles to emulating a trial protocol in observational data.

Obstacle	Common Solution												
Individuals are consistent with both treatments arms at time zero	Clone-Censor-Weight (CCW) Approach 												
Treatment switching and non-adherence occur													
Individuals are eligible for the trial at multiple times	Sequential Trials Approach ID = 1 <table data-bbox="1030 784 1245 954"><thead><tr><th>ID</th><th>Arm</th><th>Time</th><th>Event</th></tr></thead><tbody><tr><td>1</td><td>A</td><td>2</td><td>0</td></tr><tr><td>1</td><td>A</td><td>1</td><td>1</td></tr></tbody></table>	ID	Arm	Time	Event	1	A	2	0	1	A	1	1
ID	Arm	Time	Event										
1	A	2	0										
1	A	1	1										

Treatment Schedule TTEs?

- **TTE is understudied for comparing different schedules of the same repeated treatment**
- Different protocols correspond to different questions
 - Estimand, target population
 - Eligibility criteria pertaining to treatment history
- Emulation approaches?

Observational Data Structure and Notation

- Assume for each individual i , $i = 1, \dots, N$, we observe $k = 0, \dots, K_i$ data are collected at *regular, annual visits*
- Let $A_{k,i} \in \{0, 1\}$ be a binary treatment indicator and $\mathbf{L}_{k,i}$ be a vector of measured covariate values
 - Overbars indicate history: $\bar{A}_{k,i} = \{A_{0,i}, A_{1,i}, \dots, A_{k,i}\}$,
 - Particular range of history: $\bar{A}_{(k-t,k),i} = \{A_{k-t,i}, \dots, A_{k,i}\}$
 - Underlines indicate future: $\underline{A}_{k,i} = \{A_{k,i}, A_{k+1,i}, \dots, A_{K_i,i}\}$

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- In contrast to A_k , define $Z_{k,t}$ for $t \geq 1$ such that

$$Z_{k,t} = \begin{cases} 1 & \text{if } \bar{A}_{k,t} = \{A_k, A_{k+1}, \dots, A_{t-1}, A_t\} = \{1, 1, \dots, 1, 1\} \\ 0 & \text{if } \bar{A}_{k,t} = \{A_k, A_{k+1}, \dots, A_{t-1}, A_t\} = \{1, 0, \dots, I(t-1 \text{ is even}), I(t \text{ is even})\} \end{cases},$$

- Denote adherence for the duration of the study $Z = Z_{0,K_i}$

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- Denote adherence for the duration of the study $Z = Z_{0,K_i}$
- Let $\lfloor t \rfloor$ indicate the time of the most recent study visit k at or prior to continuous time t , $\lfloor t \rfloor \in \{0, 1, \dots, K_i\}$ for individual i

Emulation Approaches

- Must deal with common obstacles, plus...
 - Non-adherence at treatment *and* schedule level
 - Complex treatment schedules arm effects

Emulation Approaches

- Must deal with common obstacles, plus...
 - Non-adherence at treatment *and* schedule level
 - Complex treatment schedules arm effects
- We consider two emulation approaches, similar to Keogh et al.:
 - ① **CCW/Sequential Trials**: common to TTE literature
 - ② **MSM-IPTW**: a conventional marginal structural model with inverse-probability-of-treatment weighting
- Will handle obstacles and emulate certain elements differently
 - *Eligibility criteria*: multiple time-zeros?
 - *Treatment allocation*: how do we think about treatment?
 - *Follow-up*: censoring at non-adherence?
- Identification assumptions are the **same** for MSM-IPTW and CCW

Simulation Study Objectives

- 1 Evaluate the performance of different TTE approaches for comparing fixed schedules of the same repeated treatment
- 2 Clarify the pitfalls of common TTE analysis tools in this setting

Simulation Study Design

- We emulate **four different trial protocols** using both MSM-IPTW and CCW/Sequential Trials
- These protocols differ only in eligibility criteria pertaining to **treatment history**
 - Under MSM-IPTW, the emulation is the same for all protocols
- The Protocols:
 - Trial 1. **Any Screening History**
 - Trial 2. **No Screening for Two Years**
 - Trial 3. **No Screening for Three Years**
 - Trial 4. **Screening Naive Only**
- Estimand: per-protocol **marginal risk differences** among individuals at their first times of eligibility ($k = 0$)

Data Generating Mechanism

We generate discrete visit information for a 10-year study period, with more granular information on event times (e.g., due to a registry) for $n = 1000$ according to Figure 2.

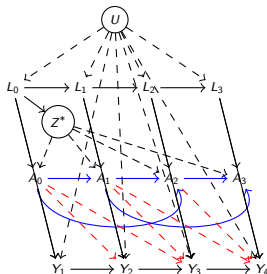


Figure 2: Directed acyclic graph (DAG) depicting relationships between L , A , discrete time outcome Y , unmeasured frailty U , and unmeasured, underlying screening pattern tendency Z^* . Red, dashed lines represent carryover effects under eq. (2).

Hazard Model 1. Without Carryover Effect

$$h(t \mid A_{[t]}, L_{[t]}, U) = \beta_0 + \beta_A A_{[t]} + \beta_L L_{[t]} + \beta_U U \quad (1)$$

Hazard Model 2. Carryover Effect – Trials 1 and 2 Get the Washout Period Wrong

$$h(t \mid A_{[t]}, \bar{A}_{([t]-2, [t]-1)}, L_{[t]}, U) = \beta_0 + \beta_A A_{[t]} + \beta_{A1} A_{[t]-1} + \beta_{A2} A_{[t]-2} + \beta_L L_{[t]} + \beta_U U \quad (2)$$

Analytical Approaches

MSM-IPTW

- Stabilized IPTW include L_0 and are consistent with Figure 2:

$$SW_i(t) = \prod_{k=1}^{\lfloor t \rfloor} \frac{P(A_k = a_{k,i} \mid L_{0,i}, \bar{A}_{(k-2,k-1),i}, T_i \geq k)}{P(A_k = a_{k,i} \mid L_{k,i}, \bar{A}_{(k-2,k-1),i}, T_i \geq k)}. \quad (3)$$

- Fitted MSM must also include L_0 :

$$h(t \mid A_0 = 1, \bar{A}_{\lfloor t \rfloor - 1}, \bar{L}_{\lfloor t \rfloor}) = \beta_0(t) + I(t \geq 1) \sum_{p=1}^{\lfloor t \rfloor} \beta_{Ap}(t) a_{\lfloor t \rfloor - p} + \beta_L(t) I_0. \quad (4)$$

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CCW/Sequential Trials

- Stabilized IPCW depend on treatment history at trial baseline:

$$SW_{i,k}^z(t-k) = \prod_{l=k+1}^{k+\lfloor t \rfloor} \frac{P(Z_l = z \mid L_{k,i}, \bar{Z}_{(k,l-1),i} = z, \bar{A}_{(k-2,k-1),i}, T_i \geq k)}{P(Z_l = z \mid L_{l,i}, \bar{Z}_{(k,l-1),i} = z, \bar{A}_{(k-2,k-1),i}, T_i \geq k)}, \quad z \in \{0, 1\}. \quad (5)$$

- Naively-fitted MSMs include an intercept, the treatment schedule, and (trial) baseline covariate

Analytical Approaches

- Counterfactual event time under regime $\mathbf{r} = (r_0, \dots, r_{K_i})$: $T^{\mathbf{a}_0=\mathbf{r}}$.
- Per-protocol **marginal risk differences** among individuals at their first times of eligibility ($k = 0$):

$$\begin{aligned}
 P(T^{\mathbf{a}_0=\{1,0,1,0,\dots\}} \leq \tau) - P(T^{\mathbf{a}_0=\mathbf{1}} \leq \tau) &= P(T^{\mathbf{a}_0=\mathbf{1}} > \tau) - P(T^{\mathbf{a}_0=\{1,0,1,0,\dots\}} > \tau) \quad (6) \\
 &= P(T^{Z=1} > \tau) - P(T^{Z=0} > \tau) \quad (7)
 \end{aligned}$$

- Both approaches use **empirical standardization**:

$$\hat{P}(T^{\mathbf{a}_0=\mathbf{r}} > \tau) = \frac{1}{n_0} \sum_{i \in C_0} \hat{P}(T^{\mathbf{a}_0=\mathbf{r}} > \tau | \bar{L}_{0,i}) = \frac{1}{n_0} \sum_{i \in C_0} \exp(-\hat{H}_{T^{\mathbf{a}_0=\mathbf{r}}}(\tau | \bar{L}_{0,i})) \quad (8)$$

where C_0 denotes the set of n_0 eligible individuals at $k = 0$.

Standardization to $k = 0$ Under Sequential Trials

- **With a Carryover Effect**, $\beta_Z(t)$ will be biased under Trials 1 and 2
- **Without a Carryover Effect?**
 - Sequential trials *changes the distribution of treatment histories at baseline* when pooling the trials together, differs from $k = 0$
 - As is, standardized estimates are *marginal over different populations!*

Treatment Naive:

$$\hat{P}(T^{a_0} > \tau | A_0 = 1, \bar{A}_{-1} = 0) = \frac{1}{n_0} \sum_{i \in C_0} \hat{P}(T^{a_0} > \tau | L_0 = l_i, A_0 = 1, \bar{A}_{-1} = 0) \quad (9)$$

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Any Screening History:

$$\hat{P}(T^{a_0} > \tau | A_0 = 1) = \frac{1}{n_0} \sum_{i \in C_0} \hat{P}(T^{a_k} > \tau | L_k = l_i, A_k = 1) \quad (10)$$

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An adjusted model allows us to marginalize over treatment history:

$$h_k(t | A_k = 1, \bar{A}_{(k-2, k-1)}, \bar{L}_k, Z) = \beta_0(t) + \beta_Z(t)z + \beta_{A1}(t)a_{k-1} + \beta_{A2}(t)a_{k-2} + \beta_L(t)l_k \quad (11)$$

$$\hat{P}(T^{a_0} > \tau | A_0 = 1, \bar{A}_{(k-2, k-1)} = 0) = \frac{1}{n_0} \sum_{i \in C_0} \hat{P}(T^{a_k} > \tau | L_k = l_i, A_k = 1, \bar{A}_{(k-2, k-1)} = 0)$$

Results

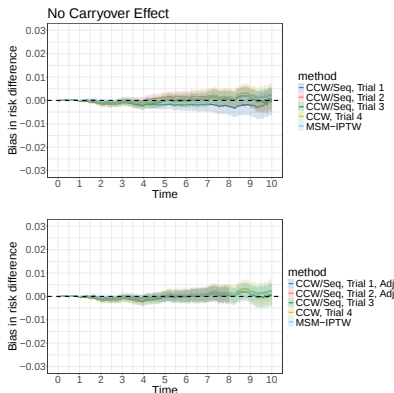


Figure 3: Bias of different emulation approaches under Hazard Model 1.

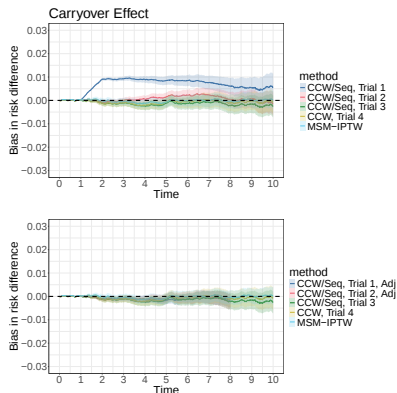


Figure 4: Bias of different emulation approaches under Hazard Model 2.

Bias for the adjusted models is truncated at time 8, as effects are inestimable afterwards.
Results are averaged over 1000 simulated datasets.

Results

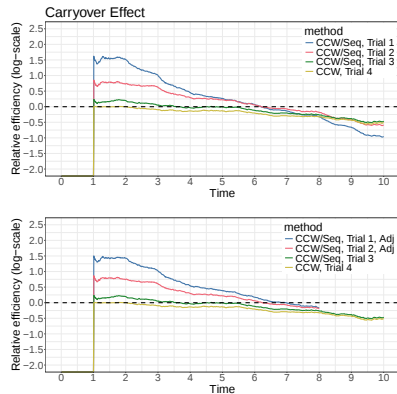
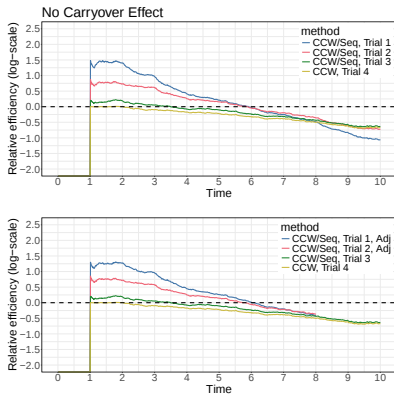


Figure 5: Relative efficiency compared with MSM-IPTW under Hazard Model 1.

Figure 6: Relative efficiency compared with MSM-IPTW under Hazard Model 2.

Efficiency for the adjusted models is truncated at time 8, as effects are inestimable afterwards.
Results are averaged over 1000 simulated datasets.

Conclusions

CCW

- 1 Relative efficiency favors MSM-IPTW late in study due to censoring at non-adherence
- 2 Requires correct functional form for *schedule arm effect*

Sequential Trials

- 1 Estimates can differ between studies with one time-zero and studies that allow multiple time-zeros
- 2 Including pre-trial treatment history in outcome models permits standardization, mitigates differences and biases
- 3 Short-term efficiency gains compared to MSM-IPTW

Discussion

- TTE is not a statistical method! Different approaches exist and may be preferred in different settings
- **Limitations**
 - Simulation assumes data are collected at regular, annual study visits
 - Assume covariate data are collected regardless of treatment status
- **Future directions**
 - Incorporate irregular and/or informative visit processes
 - Incremental causal effects (Kennedy, 2019; Ying et al., 2025)
 - Real data examples

Kennedy EH. JASA. 2019. doi: 10.1080/01621459.2017.1422737.
Ying A, et al. arXiv. 2025. 10.48550/arXiv.2409.13097

Thank you! Questions?

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Advised by Nicholas J. Seewald, PhD

Assumptions: Sequential Exchangeability

Sequential Exchangeability Under MSM-IPTW:

$$T^{\bar{a}} \perp\!\!\!\perp A_k \parallel \bar{L}_k, \bar{A}_{k-1} = \bar{a}_{k-1}, T \geq k \quad \text{for } k \in \{0 \dots 9\}.$$

This assumption only needs to hold for our two treatment strategies of interest through time k to permit identification.

$$T^Z \perp\!\!\!\perp A_k \parallel \bar{L}_k, Z_{(0,k-1)} = z, T \geq k \quad \text{for } k \in \{0 \dots 9\}, z \in \{0, 1\}. \quad (13)$$

which is equivalent to writing: (14)

$$T^Z \perp\!\!\!\perp Z_{(0,k)} \parallel \bar{L}_k, Z_{(0,k-1)} = z, T \geq k \quad \text{for } k \in \{0 \dots 9\}, z \in \{0, 1\}. \quad (15)$$

Sequential Exchangeability Under CCW:

$$T^Z \perp\!\!\!\perp Z_{(0,k)} \parallel \bar{L}_k, Z_{(0,k-1)} = z, T \geq k \quad \text{for } k \in \{0 \dots 9\}, z \in \{0, 1\}$$

Data Generating Mechanism

Table 2: Hazard Model Parameters by Simulation Setting

	Primary Simula- tion	Decaying Hazards	Low Hazards Simulation
Parameters in Both Models	$\beta_L = 0.005625$ $\beta_U = 0.005625$	$\beta_L = 0.005625$ $\beta_U = 0.005625$	$\beta_L = 0.001875$ $\beta_U = 0.001875$
Model Without Carryover Effect	$\beta_0 = 0.12$ $\beta_A = -0.03$	$\beta_0 = 0.12$ $\beta_A = -0.0375$	$\beta_0 = 0.04$ $\beta_A = -0.01$
Model With Car- ryover Effect	$\beta_0 = 0.15$ $\beta_A = -0.03$ $\beta_{A1} = -0.03$ $\beta_{A2} = -0.03$	$\beta_0 = 0.015$ $\beta_A = -0.045$ $\beta_{A1} = \beta_A(1 - \frac{11}{36})$ $\beta_{A2} = \beta_{A1}(1 - \frac{11}{36})$	$\beta_0 = 0.05$ $\beta_A = -0.01$ $\beta_{A1} = -0.01$ $\beta_{A2} = -0.01$

Data Generating Mechanism

The generated population of data, indexed by $j = 0, \dots, 9$, is re-aligned such that an individual's first treatment is at $k = 0$; can be at different calendar times for different i .

	id	A	L	L.baseline	time	time.stop	event
1	2	0	-0.6553571	-0.6553571	0	1	0
2	2	0	0.1494684	-0.6553571	1	2	0
3	2	0	2.2511630	-0.6553571	2	3	0
4	2	1	0.5501216	-0.6553571	3	4	0
5	2	0	0.2920004	-0.6553571	4	5	0
6	2	1	-1.0730618	-0.6553571	5	6	0
7	2	0	-2.9149301	-0.6553571	6	7	0
8	2	1	-1.4522084	-0.6553571	7	8	0
9	2	0	-2.6129599	-0.6553571	8	9	0
10	2	1	-1.1481563	-0.6553571	9	10	0

Set Study Baseline at $j=3$



	id	A	L	L.baseline	time	time.stop	event
1	2	1	0.5501216	0.5501216	0	1	0
2	2	0	0.2920004	0.5501216	1	2	0
3	2	1	-1.0730618	0.5501216	2	3	0
4	2	0	-2.9149301	0.5501216	3	4	0
5	2	1	-1.4522084	0.5501216	4	5	0
6	2	0	-2.6129599	0.5501216	5	6	0
7	2	1	-1.1481563	0.5501216	6	7	0

Figure 7: Realignment of generated data for analysis.

Data Generating Mechanism: Screening Patterns

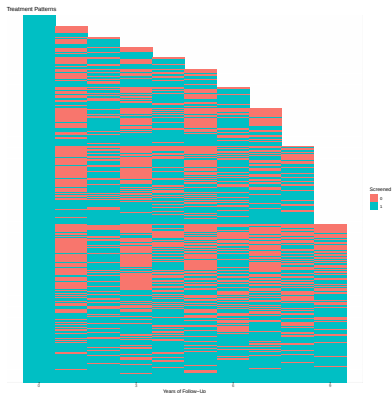


Figure 8: Heatmap of screening patterns for one randomly selected iteration, under Hazard Model 1.

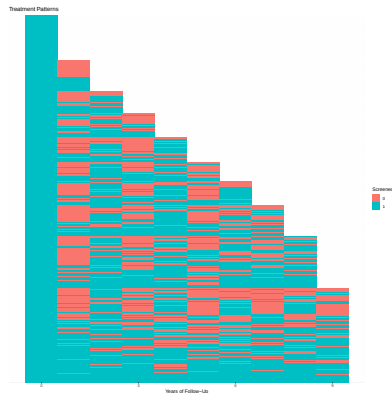


Figure 9: Heatmap of screening patterns for one randomly selected iteration, under Hazard Model 2.

Data Generating Mechanism: Screening Patterns

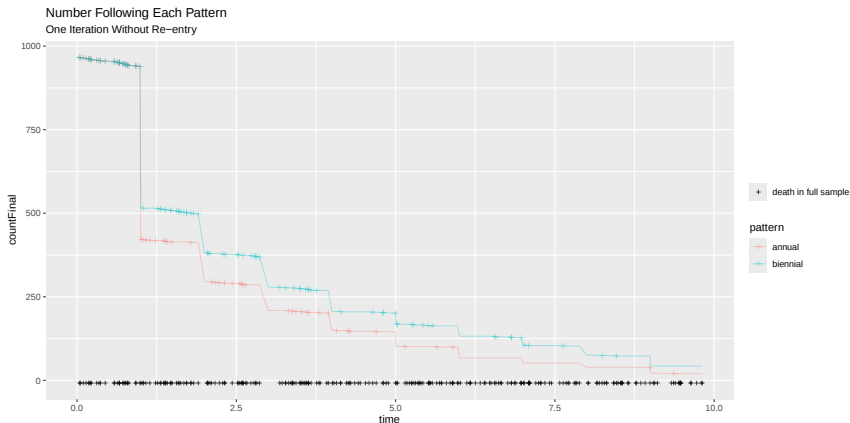


Figure 10: Rugplot of annual and biennial arms for one randomly selected iteration, under Hazard Model 1.

Data Generating Mechanism: Screening Patterns

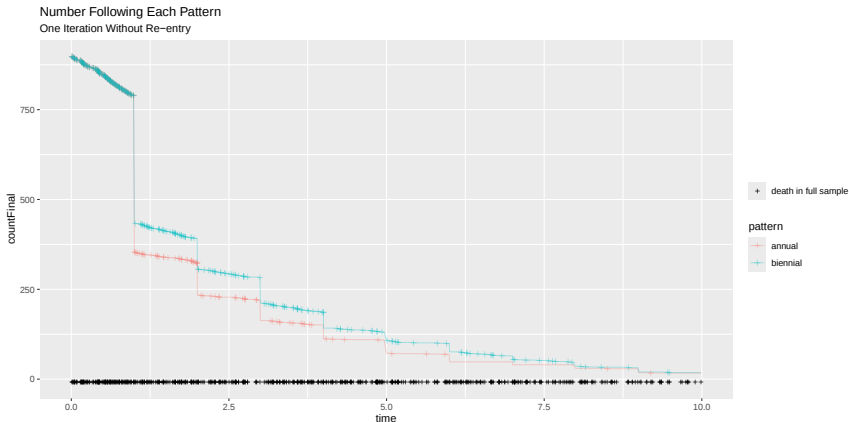


Figure 11: Rugplot of annual and biennial arms for one randomly selected iteration, under Hazard Model 2.

Additional Results, Original Settings

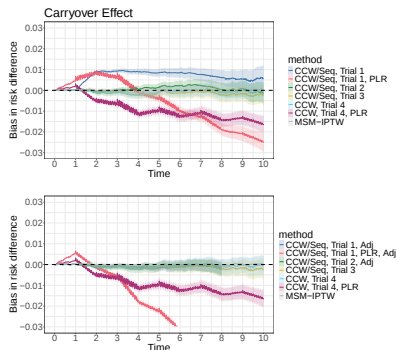
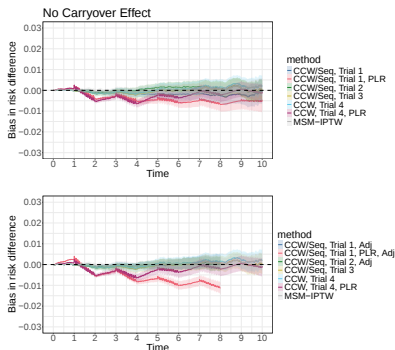


Figure 12: Bias of different emulation approaches, including pooled linear models, under Hazard Model 1.

Figure 13: Bias of different emulation approaches, including pooled linear models, under Hazard Model 2.

Additional Results, Original Settings

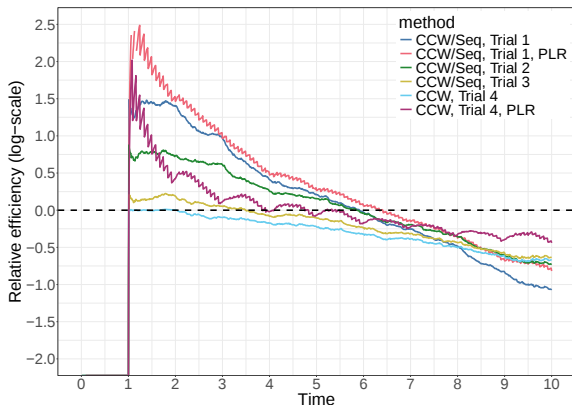


Figure 14: Relative efficiency of analytical approaches, including pooled linear models, compared with MSM-IPTW under Hazard Model 1.

Additional Results, Decaying Hazards

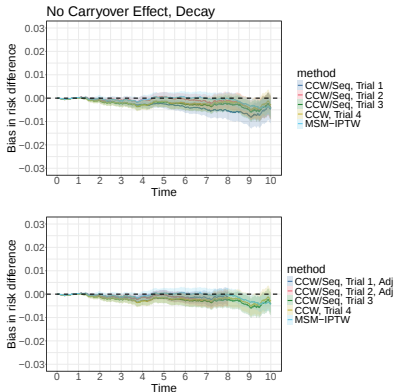


Figure 15: Bias of different emulation approaches under Hazard Model 3, where the treatment effect decays over time.

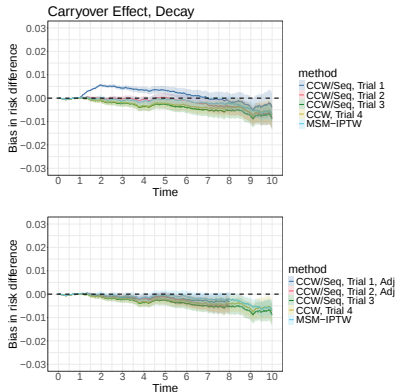


Figure 16: Bias of different emulation approaches under Hazard Model 4, where the treatment effect decays over time.

Simulation: Varied Treatment Histories at Baseline

- **Objective:** verify that the comparability of MSM-IPTW and CCW (when eligibility is not re-assessed) is not specific to the population at $k = 0$ being treatment-naïve.
- Let some individuals be treatment-naïve at time-zero, while letting others be treated three years ago
- To avoid differential immortal time bias: generate three pre-baseline visits for all individuals, require no event in this period for eligibility
- Estimates under both analytical approaches will be marginal to the population at $k = 0$, regardless of the distribution of treatment history in that baseline population
- When eligibility after previous treatment is permitted and a sequence of trials is emulated, the distribution of treatment histories pooled over all trial baselines will still look different

Simulation: Varied Treatment Histories at Baseline

$$U \sim N(0, 1)$$

$$L_0 | U \sim N(U, 1)$$

$$Z^* | L_0 \sim \text{Bern}\left(\text{expit}(\tau_0 + \tau_L L_0)\right)$$

$$A_0 \sim \text{Bern}(0.2). \text{ Set } A_1, A_2 = 0.$$

For $j = 1, 2$ (pre-baseline visits):

- $L_j | L_{j-1}, A_{j-1}, j, U \sim N\left(\delta_0 + \delta_L L_{j-1} + \delta_A A_{j-1} + \delta_T j + U, 1\right)$

For $j = 3, 4, \dots, 12$ (study visits):

- $L_j | L_{j-1}, A_{j-1}, j, U \sim N\left(\delta_0 + \delta_L L_{j-1} + \delta_A A_{j-1} + \delta_T j + U, 1\right)$

- $A_j | A_{j-1}, A_{j-2}, L_j, Z^* \sim \text{Bern}\left(\text{expit}(\beta_0 + \beta_1 A_{j-1} + \beta_2 A_{j-2} + \beta_3 A_{j-1} Z^* + \beta_4 A_{j-2} Z^* + \beta_L L_j + \beta_Z Z^*)\right)$

Additional Results, Varied Treatment Histories at Baseline

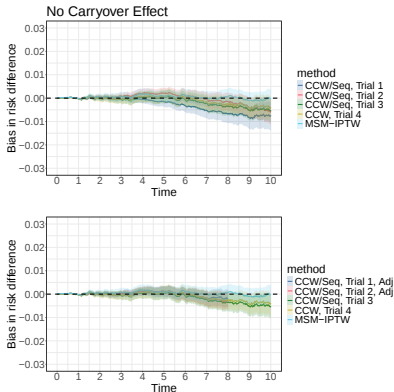


Figure 17: Bias of different emulation approaches under Hazard Model 1 when there are variable treatment histories at baseline.

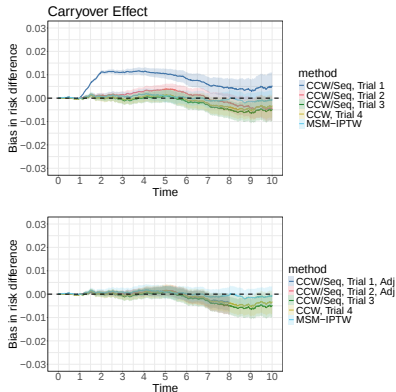


Figure 18: Bias of different emulation approaches under Hazard Model 2 when there are variable treatment histories at baseline.

Supplemental slides
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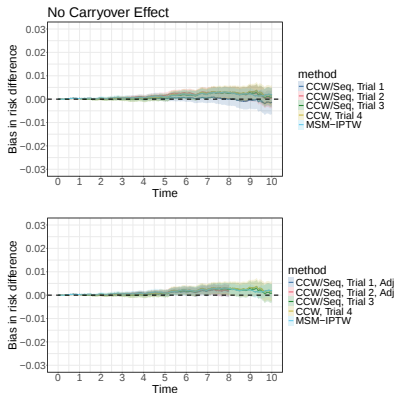


Figure 19: Bias of different emulation approaches under Hazard Model 1 with lower hazards.

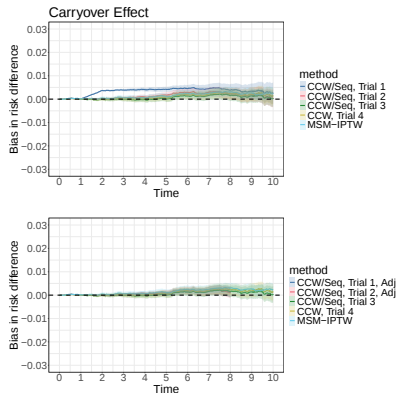


Figure 20: Bias of different emulation approaches under Hazard Model 2 with lower hazards.

Connecting Model Forms: An Aside

- For MSM-IPTW, for times $t \in [2, 3)$, the design matrix is given by:

$$\mathbf{X}_i(t) = \mathbf{Y}_{t,i}^R(1, A_{1,i}(t), A_{2,i}(t), L_{0,i})$$

Consider the following steps:

- Re-parameterize* the MSM-IPTW model based on regime indicators, for example for times $t \in [2, 3)$:

$$h(t \mid A_0 = 1, \bar{A}_{[t]-1}, \bar{L}_{[t]}) = \gamma_0(t)I(A_0 = 1, A_1 = 0, A_2 = 1) + \gamma_1(t)I(A_0 = 1, A_1 = 1, A_2 = 0) + \gamma_2(t)I(A_0 = 1, A_1 = 0, A_2 = 0) + \gamma_3(t)I(A_0 = 1, A_1 = 1, A_2 = 1) + \gamma_L(t)L_0. \quad (16)$$

This results in design matrix:

$$\mathbf{X}_i(t) = \mathbf{Y}_{t,i}^R(I(A_{0,i} = 1, A_{1,i} = 0, A_{2,i} = 1), I(A_{0,i} = 1, A_{1,i} = 1, A_{2,i} = 0), I(A_{0,i} = 1, A_{1,i} = 0, A_{2,i} = 0), I(A_{0,i} = 1, A_{1,i} = 1, A_{2,i} = 1), L_{0,i}) \quad (17)$$

- Subset* the data to those consistent with the annual or biennial regime through time t :

$$\begin{aligned} \mathbf{X}_i(t) &= \mathbf{Y}_{t,i}^R(I(A_{0,i} = 1, A_{1,i} = 0, A_{2,i} = 1), I(A_{0,i} = 1, A_{1,i} = 1, A_{2,i} = 1), L_{0,i}) \\ &= \mathbf{Y}_{t,i}^R(I(Z_i = 0), I(Z_i = 1), L_{0,i}) \Rightarrow \mathbf{Y}_{t,i}^R(1, Z_i, L_{0,i}) \end{aligned}$$

- The role of baseline covariate distributions and collapsibility