Estimating treatment effects with competing intercurrent events in randomized controlled trials

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Overview

Motivating randomized controlled trials (RCTs)

Causal parameter of interest

Assumption and identification

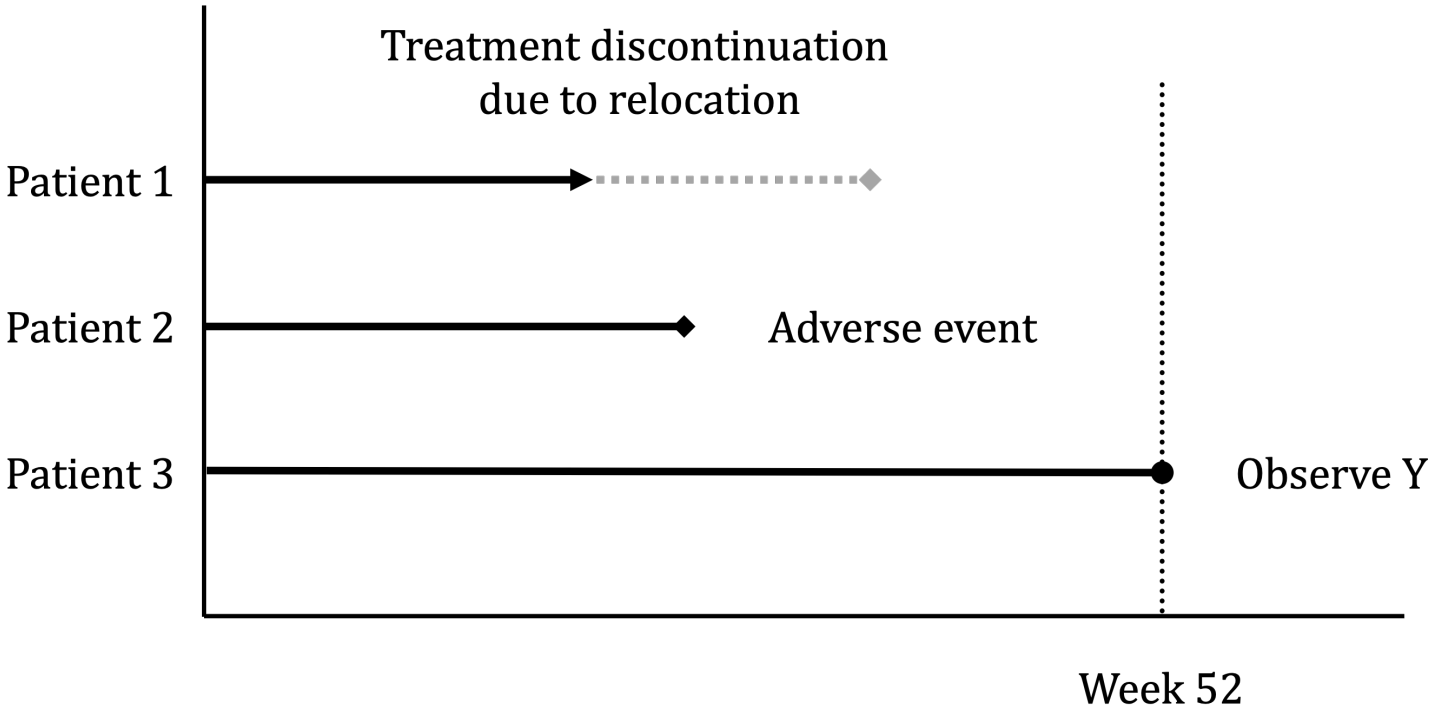
From basic estimators to augmented, robust estimators

Real-world application

Motivating example: two phase-3 immunology trials

- Morand et al. (2023) and Petri et al. (2023)
- Causal effect of baricitinib versus placebo on Systemic Lupus Erythematosus
- Primary endpoint: an immune response index measured *52 weeks after* treatment initiation
- Ideally, comparisons between two groups
- Outcomes not measured: 218/760 and 211/775 in two trials

Motivating example: two phase-3 immunology trials



- Treatment discontinuation due to relocation and adverse event in the example are called intercurrent events (ICEs)
- ICEs: events that occur *after* the treatment initiation and *affect* either the interpretation or existence of outcome measurements

ICEs in the motivating RCTs

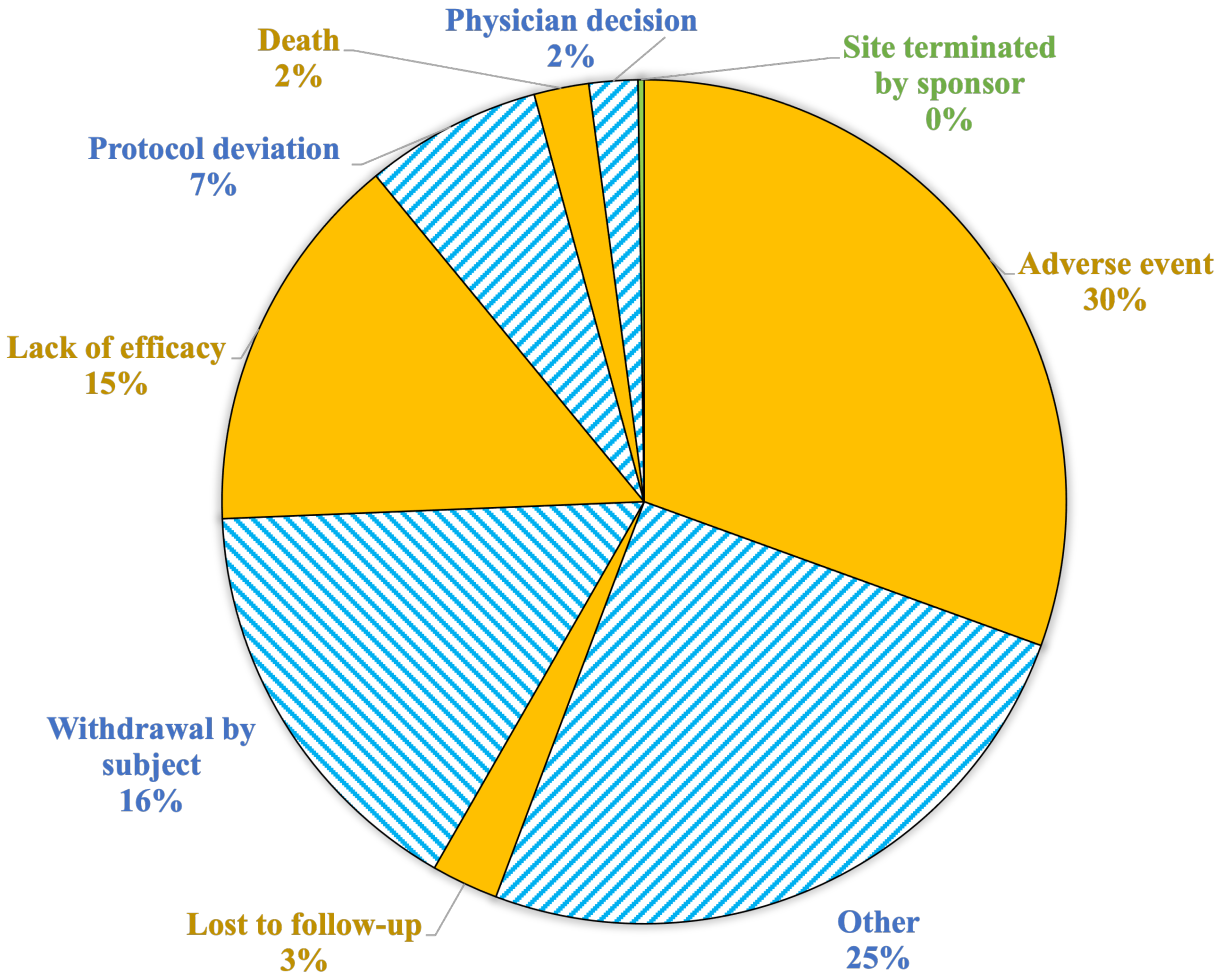


Figure: Pie chart showing the ICE types and proportions

Five strategies to address ICEs

- ICH E9 (R1): a guideline published in 2019 to address ICEs by the International Council for Harmonisation (ICH)
- Treatment policy strategy: intention-to-treat-type principle
- Hypothetical strategy: what if hypothetically the ICE would not occur
- Composite outcome strategy: modify the causal parameter of interest
  - an ICE is itself informative about the patients' outcome of interest
  - e.g., when the outcome is success or failure, the occurrence of ICE can be treated as another mode of failure
- While-on-treatment strategy: compare outcomes before ICEs
- Principal stratification strategy: causal effects on subgroups

Our proposal: combine two strategies

- Classify ICEs into two broad types:
  - effect-informative ICEs, e.g., adverse effect, lack of efficacy
  - effect-uninformative ICEs, e.g., treatment discontinuation due to relocation or COVID-19 lockdown
- Combining composite outcome and hypothetical strategies
  - effect-informative ICEs: composite outcome strategy
  - effect-uninformative ICEs: hypothetical strategy
- Key challenges:
  - combining composite outcome and hypothetical strategies needs new theory and method
  - need to deal with competing ICEs

Challenge in combining the two strategies

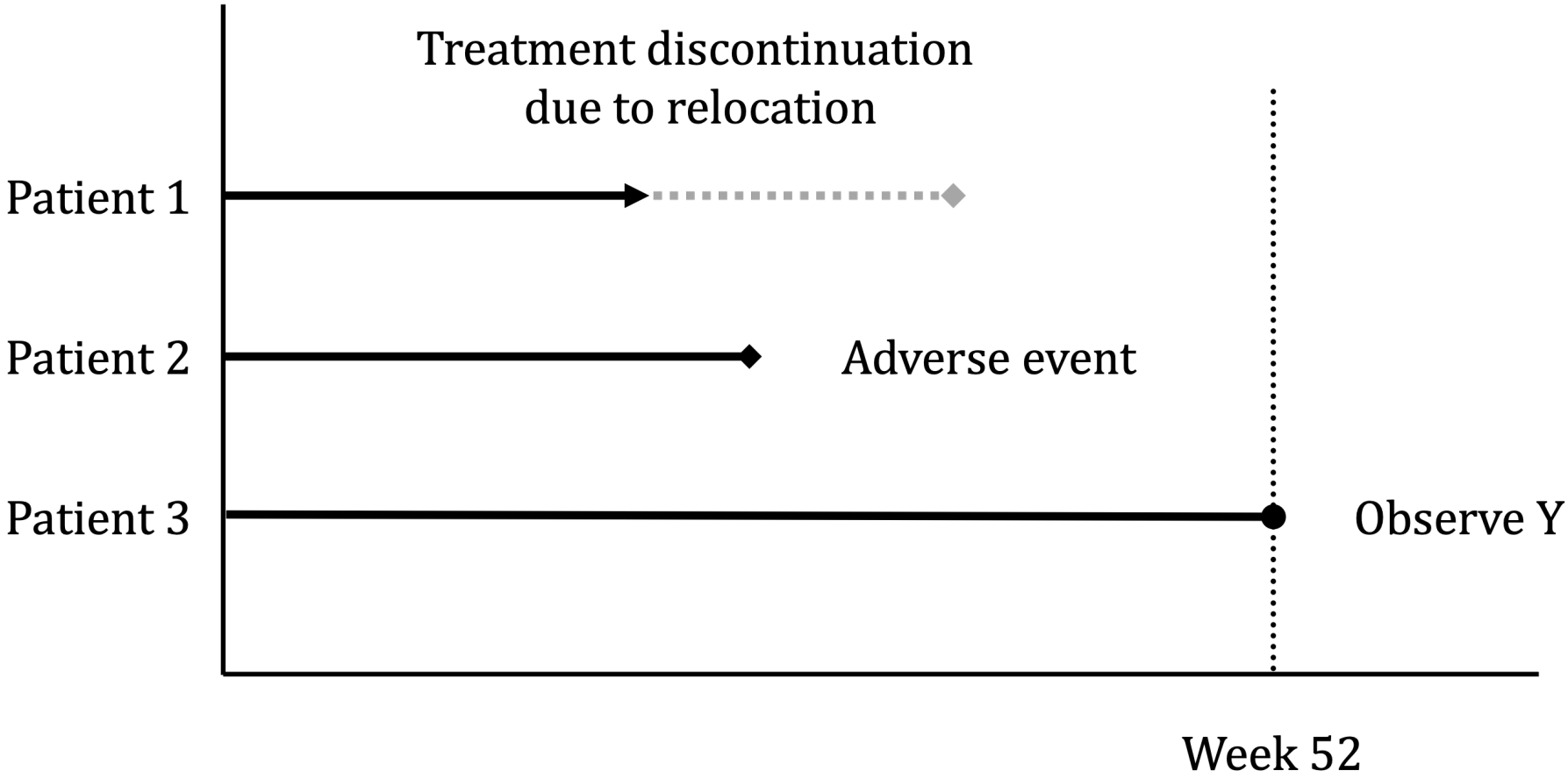


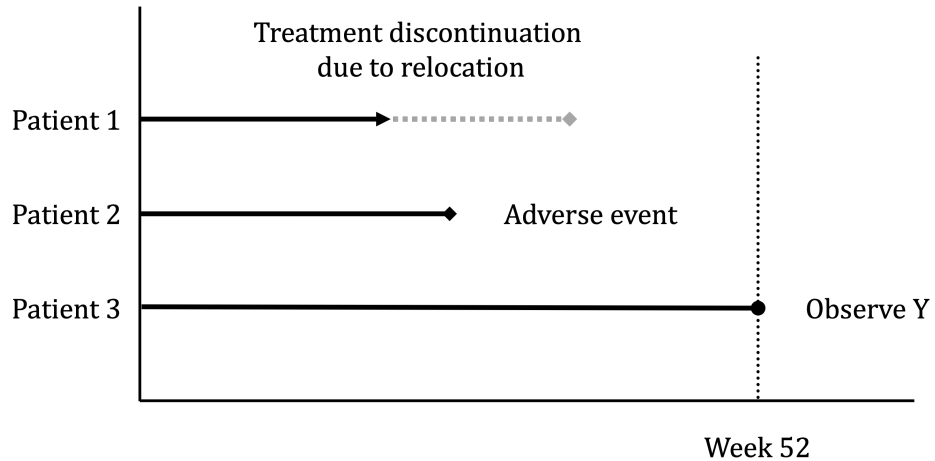
Figure: Illustration of the motivating immunology trial example

Notation and potential outcomes

- Binary treatment: $A = 1, 0$ for treatment and control
- Primary endpoint: Y, measured at a pre-specified time point k
- Two types of ICEs:
  - effect-informative ICEs: event time T
  - effect-uninformative ICEs: event time C
- Define $T = \infty$ if $T > k$, and $C = \infty$ if $C > k$
- Both ICEs are *post-treatment* variables, thus having potential values $T(a)$ and $C(a)$
- Potential outcomes: $Y(a, t, c)$
- Consistency: the observed outcome $Y = Y(A, T(A), C(A))$

Causal parameter of interest

$$\tau = E[\underbrace{Y(1, c = \infty)}_{\text{hypothetical}} \underbrace{1\{T(1) = \infty\}}_{\text{composite}}] - E[Y(0, c = \infty)\, 1\{T(0) = \infty\}]$$



observed ICE types	(T, C, k)-relationship	$Y(A, c = \infty)$	$1(T = \infty)$	composite outcome
TD	$T \wedge k > C$	?	?	?
AE	$C \wedge k > T$	?	0	0
no AE/TD	$C \wedge T > k$	Y	1	Y

Identification assumptions

Assumption 1 (Randomization)

$A \perp\!\!\!\perp \{Y(a, c = \infty), T(a), C(a)\} \mid X$ *for* $a = 0, 1$.

- Guaranteed by the experimental design in a randomized trial

Identification assumptions

Assumption 1 (Randomization)

$A \perp\!\!\!\perp \{Y(a, c = \infty), T(a), C(a)\} \mid X$ *for* $a = 0, 1$.

- Guaranteed by the experimental design in a randomized trial

Assumption 2 (Effect-uninformative ICE time)

$C(a) \perp\!\!\!\perp \{Y(a, c = \infty), T(a)\} \mid X$ *for* $a = 0, 1$.

- Time to treatment discontinuation due to relocation is independent of the hypothetical potential outcome and the time to adverse effect given baseline covariates

Nonparametric identification

Theorem 1 (Nonparametric identification)

Under Assumptions 1 and 2, τ is nonparametrically identified by the following identification formulas:

$$\tau = E\left\{\mu_1(X)S_1(k \mid X) - \mu_0(X)S_0(k \mid X)\right\} \quad (1)$$

$$= E\left[\frac{AY1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{(1-A)Y1(T \wedge C > k)}{\{1-e(X)\}\, G_0(k \mid X)}\right]. \quad (2)$$

Nonparametric identification 1: outcome models

$$\tau = E\left\{\mu_1(X)S_1(k \mid X) - \mu_0(X)S_0(k \mid X)\right\}, \tag{1}$$

where

- $\mu_a(X) = E(Y \mid T \wedge C > k, X, A = a)$: conditional mean of observed outcome in the subsample with no ICE and $A = a$, and

Nonparametric identification 1: outcome models

$$\tau = E\left\{\mu_1(X)S_1(k \mid X) - \mu_0(X)S_0(k \mid X)\right\}, \tag{1}$$

where

- $\mu_a(X) = E(Y \mid T \wedge C > k, X, A = a)$, and
- $S_a(k \mid X) = \text{pr}(T > k \mid X, A = a)$: survival probability of AE time larger than k in the subsample $A = a$ conditional on covariates

Nonparametric identification 2: weighting

$$\tau = E\left[\frac{AY1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{(1-A)Y1(T \wedge C > k)}{\{1-e(X)\}G_0(k \mid X)}\right], \qquad (2)$$

where

- $e(X) = \text{pr}(A = 1 \mid X)$: propensity score, and

Nonparametric identification 2: weighting

$$\tau = E\left[\frac{AY1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{(1-A)Y1(T \wedge C > k)}{\{1-e(X)\}\, G_0(k \mid X)}\right], \tag{2}$$

where

- $e(X) = \text{pr}(A = 1 \mid X)$, and
- $G_a(k \mid X) = \text{pr}(C > k \mid X, A = a)$: conditional probability of not censoring up until time k in the subsample $A = a$

Nonparametric identification

$$\tau = E\left\{\mu_1(X)S_1(k \mid X) - \mu_0(X)S_0(k \mid X)\right\} \quad (1)$$

$$= E\left[\frac{AY1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{(1-A)Y1(T \wedge C > k)}{\{1-e(X)\}\, G_0(k \mid X)}\right]. \quad (2)$$

- $\mu_a(X) = E(Y \mid T \wedge C > k, X, A = a)$
- $S_a(k \mid X) = \text{pr}(T > k \mid X, A = a)$
- $e(X) = \text{pr}(A = 1 \mid X)$
- $G_a(k \mid X) = \text{pr}(C > k \mid X, A = a)$
- Identification of $S_a(t \mid X)$ and $G_a(t \mid X)$ for $t \leq k$ (Robin and Rotnitzky, 1992; Robins and Finkelstein, 2000)

Two basic estimators based on two identification formulas

- Outcome regression estimator:

$$\hat{\tau}^{\text{out}} = n^{-1} \sum_{i=1}^{n} \hat{\mu}_1(X_i) \hat{S}_1(k \mid X_i) - n^{-1} \sum_{i=1}^{n} \hat{\mu}_0(X_i) \hat{S}_0(k \mid X_i)$$

- Inverse propensity score weighting estimator:

$$\hat{\tau}^{\text{ipw}} = n^{-1} \sum_{i=1}^{n} \frac{A_i Y_i 1(T_i \wedge C_i > k)}{\hat{e}(X_i) \hat{G}_1(k \mid X_i)} - n^{-1} \sum_{i=1}^{n} \frac{(1 - A_i) Y_i 1(T_i \wedge C_i > k)}{\{1 - \hat{e}(X_i)\} \hat{G}_0(k \mid X_i)}$$

- $\hat{\tau}^{\text{out}}$: consistent if the subsample outcome model and the survival function are correctly specified
- $\hat{\tau}^{\text{ipw}}$: consistent if the propensity score model and the censoring mechanism are correctly specified

An augmented, conditionally doubly robust estimator

- Similar to the classic doubly robust estimator by combining outcome regression and inverse propensity score weighting
- Augment weighting by outcome regression:

$$\hat{\tau}^{\text{aug}} = \hat{\tau}^{\text{ipw}} - n^{-1} \sum_{i=1}^{n} \left\{ \frac{A_i - \hat{e}(X_i)}{\hat{e}(X_i)} \hat{\mu}_1(X_i) \hat{S}_1(k \mid X_i) + \frac{A_i - \hat{e}(X_i)}{1 - \hat{e}(X_i)} \hat{\mu}_0(X_i) \hat{S}_0(k \mid X_i) \right\}.$$

- Conditionally doubly robust: Assume $G_a(k \mid X)$ is correct for $a = 0, 1$. $\hat{\tau}^{\text{aug}}$ is consistent for τ if either $e(X)$ is correct, or both $\mu_a(X)$ and $S_a(k \mid X)$ are correct for $a = 0, 1$
- $\hat{\tau}^{\text{aug}}$ improves $\hat{\tau}^{\text{ipw}}$ but may not improve $\hat{\tau}^{\text{out}}$

Another augmented, doubly robust, and semiparametrically efficient estimator, based on efficient influence function

$$\hat{\tau}^{\text{eif}} = \hat{\tau}^{\text{aug}} + n^{-1} \sum_{i=1}^{n} \frac{A_i}{\hat{e}(X_i)} \hat{\mu}_1(X_i) \hat{S}_1(k \mid X_i) \int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_1}(t)}{\hat{S}_1(t \mid X_i)\, \hat{G}_1(t \mid X_i)}$$
$$- n^{-1} \sum_{i=1}^{n} \frac{1 - A_i}{1 - \hat{e}(X_i)} \hat{\mu}_0(X_i) \hat{S}_0(k \mid X_i) \int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_0}(t)}{\hat{S}_0(t \mid X_i)\, \hat{G}_0(t \mid X_i)} .$$

- $\tilde{T}_i = C_i \wedge T_i \wedge k$ and $\Delta_i = 1(C_i \geq T_i \wedge k)$
- Further augmentation based on martingales: $\mathrm{d}M_{G_a}(t) = 1(C \in (t, t + \mathrm{d}t], \Delta = 0) - 1(\tilde{T} \geq t)\mathrm{d}\Lambda_a(t \mid X)$ with $\Lambda_a(t \mid X)$ denoting the conditional cumulative hazard function for the effect-uninformative ICE C in the treatment group $A = a$ for $a = 0, 1$

Double robustness and semiparametric efficiency

- $\hat{\tau}^{\text{eif}}$ is doubly robust in the sense that it is consistent for τ if either
  - $\mu_a(X)$ and $S_a(t \mid X)$ are correct for $t \leq k$ and $a = 0, 1$; or
  - $e(X)$ and $G_a(t \mid X)$ are correct for $t \leq k$ and $a = 0, 1$
- $\hat{\tau}^{\text{eif}}$ improves the previous three estimators in terms of robustness
- Asymptotically linear and achieves the semiparametric efficiency bound

Real-world application

- Two double-blinded, randomized, placebo-controlled phase-3 immunology trials
- Effect of baricitinib on systemic lupus erythematosus
- Doses: 2mg baricitinib, 4mg baricitinib, and placebo
- Primary outcome: Systemic lupus erythematosus Responder Index 4 (SRI4) at week 52, a binary composite responder index based on:
  - improvement in disease activity, and
  - without worsening of the overall condition or the development of substantial disease activity in new organ systems
- Effect-informative ICEs: 82.6% and 84.4%; and effect-uninformative ICEs: 17.4% and 15.6%
- Covariates: geographic region, corticosteriod use, Physician's Global Assessment score

Data analysis results

		Trial 1 (Petri et al., 2023)				Trial 2 (Morand et al., 2023)			
		$\hat{\tau}^{\text{out}}$	$\hat{\tau}^{\text{ipw}}$	$\hat{\tau}^{\text{aug}}$	$\hat{\tau}^{\text{eif}}$	$\hat{\tau}^{\text{out}}$	$\hat{\tau}^{\text{ipw}}$	$\hat{\tau}^{\text{aug}}$	$\hat{\tau}^{\text{eif}}$
2mg	point	0.030	0.029	0.026	0.026	0.019	0.019	0.022	0.022
	se	0.042	0.043	0.042	0.043	0.042	0.043	0.043	0.042
	p-value	0.479	0.504	0.534	0.540	0.643	0.662	0.602	0.606
4mg	point	0.113	0.120	0.115	0.113	−0.002	−0.002	−0.002	−0.002
	se	0.046	0.046	0.046	0.046	0.042	0.042	0.042	0.042
	p-value	0.013	0.008	0.012	0.013	0.961	0.962	0.966	0.969

- Coherent results across estimators: no severe model misspecification
- Different from ad hoc methods (details in the paper)
- Incoherent results from two trials: negative results for drug approval

Thank you very much!

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Simulation

	$\hat{\tau}^{\text{out}}$			$\hat{\tau}^{\text{ipw}}$			$\hat{\tau}^{\text{aug}}$			$\hat{\tau}^{\text{eif}}$		
	Bias	SD	CR	Bias	SD	CR	Bias	SD	CR	Bias	SD	CR
all_correct	0.003	0.100	0.989	0.005	0.154	0.977	0.004	0.152	0.980	0.004	0.110	0.982
e_wrong	−0.002	0.134	0.978	−0.338	0.527	0.916	−0.003	0.479	0.961	0.000	0.234	0.979
e_G_wrong	−0.002	0.130	0.985	−0.194	1.591	0.831	0.141	1.559	0.972	−0.013	0.354	0.969
μ_S_wrong	−0.085	0.170	0.936	−0.009	0.186	0.974	−0.009	0.186	0.974	−0.012	0.176	0.972
all_wrong	0.230	0.233	0.837	0.660	5.799	0.898	0.850	5.782	0.967	0.573	3.022	0.919

Semiparametric efficient influence function (EIF)

Theorem 2 (EIF for μ_1)

Under the nonparametric model with Assumptions 1 and 2, the EIF for μ_1 is

$$
\begin{aligned}
D_{\mu_1} \quad = \quad & \frac{A}{e(X)} \left\{ \frac{Y 1(T \wedge C > k)}{G_1(k \mid X)} + \mu_1(X) S_1(k \mid X) \int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X) G_1(t \mid X)} \right\} \\
& - \frac{A - e(X)}{e(X)} \mu_1(X) S_1(k \mid X) - \mu_1, \qquad (3)
\end{aligned}
$$

- $\tilde{T} = T \wedge C \wedge k$: the observed event time;
- $\mathrm{d}M_{G_1}(t) = 1(C \in (t, t + \mathrm{d}t], \Delta = 0) - 1(\tilde{T} \geq t)\mathrm{d}\Lambda_1(t \mid X)$: the martingale constructed from the censoring counting process;
- $\Lambda_1(t \mid X)$: the conditional cumulative hazard function for the censoring C in the treatment subgroup.

EIF estimator

With discrete observed time points, the integration part for i:

$$\int_0^{\tilde{T}_i} \frac{\mathrm{d}M_{\hat{G}_1}(t)}{\hat{S}_1(t \mid X_i)\hat{G}_1(t \mid X_i)} = \sum_{t \le \tilde{T}_i} \frac{1(\Delta_i = 0, C_i = t) - \hat{\lambda}_{C_1}(t \mid X_i)}{\hat{S}_1(t \mid X_i)\hat{G}_1(t \mid X_i)}$$

$$= -\sum_{t \le \tilde{T}_i} \frac{\hat{\lambda}_{C_1}(t \mid X_i)}{\hat{S}_1(t \mid X_i)\hat{G}_1(t \mid X_i)} + \frac{1(\Delta_i = 0)}{\hat{S}_1(\tilde{T}_i \mid X_i)\hat{G}_1(\tilde{T}_i \mid X_i)}. \quad (4)$$

- $\hat{\lambda}_{C_1}(t \mid X_i)$: estimated conditional hazard of censoring;
- First term in (4): summation of $-\hat{\lambda}_{C_1}(t \mid X_i)/\{\hat{S}_1(t \mid X_i)\hat{G}_1(t \mid X_i)\}$ over all observed event time points before $\tilde{T}_i$.
- Second term in (4):
  - 0 for observations that are not right-censored by LF;
  - $1/\{\hat{S}_1(\tilde{T}_i \mid X_i)\hat{G}_1(\tilde{T}_i \mid X_i)\}$ for observations with an LF event happened at time $\tilde{T}_i$.