Multiply robust estimation of causal effects with noncompliance and time-to-event outcomes

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Background: pragmatic trials

- Pragmatic trials often compare interventions or alternative delivery approaches to evaluate impact on outcomes under routine practice conditions

- Challenges arise as we move toward pragmatism
  - PRECIS-II
  - treatment effect estimands as increasingly important concept

- Many pragmatic trials report null intention-to-treat (ITT) effect

- Provide an example to go beyond ITT estimand in a recent pragmatic trial with survival outcome

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An example: ADAPTABLE pragmatic trial

- ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) is a pragmatic trial to study the effectiveness of two aspirin dosing strategies for patients with established cardiovascular diseases\(^2\).

- **Treatment assignment:** 81-mg v.s. 325-mg aspirin dosage

- **Outcome:** a composite outcome of death from any cause and hospitalization for stroke or myocardial infraction (time-to-event)

- **Complication:** not all patients take the assigned aspirin dosage.

Average treatment effect

- **Baseline covariates:** age, gender, race, ethnicity, medical and diseases history, aspirin dosage use prior to the trial, *etc.*

- Up until the maximum follow-up time (38 months after randomization), the outcome occurred in 7.5% and 7.4% of participants in the 81-mg arm and the 325-mg arm, respectively.
  - relatively rare events

- As expected, the primary analysis found a **null average treatment effect**

- To confirm no overall effect, we applied a covariate-adjusted approach to report the ITT effect
  - augmented estimator for the causal survival curves ([Bai et al, 2013; Zhang and Schaubel, 2012](#))
Figure: The ITT effects and corresponding survival probability curve, ADAPTABLE trial, 2016–2020. The ITT effects are obtained based on the doubly robust estimator by Bai et al. (2013)³.

Motivating questions

Recognizing the potential impact of noncompliance

▶ Is one specific aspirin dosage more effective than the other among compliers?

▶ the treatment efficacy

▶ Is there treatment effect heterogeneity among patients with different compliance behaviour types that contribute to the null ITT effect?

▶ ‘direct effect’ of treatment assignment (possibly due to other mechanisms that are unmeasured)

▶ To what extent the study results are sensitive to unverifiable assumptions?

Goal: seek model-robust methods and sensitivity strategies to address noncompliance with a survival outcome
Notation

Data structure

- $X$: pre-treatment covariates
- $Z$: treatment assignment (1 if 325-mg aspirin and 0 if 81-mg aspirin)
- $S$: actual treatment received
- $T$: survival time of interest—partially observed due to right censoring. Instead, we only observe $\left( U, \delta \right) = \left( \min(T, C), \mathbb{I}(T \leq C) \right)$, where $C$ is the censoring time

Pursue potential outcomes framework and define

- $S(z)$: the potential value of $S$ when setting the assignment to $z \in \{0, 1\}$.
- $T(z)$ & $C(z)$: the potential value of $T$ and $C$ when setting the assignment to $z \in \{0, 1\}$. 
Estimands

- Under the principal stratification framework, we partition the study population into 4 principal strata, based on the joint potential values $G = \{S(1), S(0)\}$:
  - $G = \{1, 1\}$: always high-dose (325-mg) takers
  - $G = \{0, 0\}$: always low-dose (81-mg) takers
  - $G = \{1, 0\}$: compliers
  - $G = \{0, 1\}$: defiers

- abbreviate the above four principal strata as $\{a, n, c, d\}$, respectively.

- Define the **Principal Survival Causal Effect (PSCE)**:
  \[
  \Delta_g(u) = S_{1,g}(u) - S_{0,g}(u)
  \]

  where $S_{z,g} = \mathbb{P}(T(z) > u|G = g)$ and $g \in \{a, n, c, d\}$.

  - $\Delta_c(u)$: ‘efficacy’ of the treatment in the ideal compliance condition.
  - $\Delta_a(u)$ and $\Delta_n(u)$: ‘direct effect’ due to treatment assignment
  - do not pursue strata-specific HR as estimands
Assumptions

Five structural assumptions to identify the PSCE.

Set I: standard assumptions in causal survival analysis (Chen et al, 2001; Zhang and Schaubel, 2012; Bai et al. 2013)

A1. (SUTVA) For all $i$, we have $S_i(z) = S_i$, $T_i(z) = T_i$, and $C_i(z) = C_i$ if patient $i$ was assigned to treatment $Z_i = z$.

A2. (Conditional randomization) $\{T(1), T(0), S(1), S(0)\} \perp Z|X$.

▶ in ADAPTABLE, a stronger version, $\{T(1), T(0), S(1), S(0), X\} \perp Z$, is satisfied by study design.

▶ use a more general assumption to allow considerations of conditional randomized trials and observational studies.

A3. (Covariate-dependent censoring) $T(z) \perp C(z)|\{Z = z, S, X\}$.
Assumptions - cont’d

Set II: additional assumptions

A4. (Monotonicity) $S_i(1) \geq S_i(0)$ for all $i$.
   ▶ excludes defiers and can be plausible for ADAPTABLE

A5. (Prinicipal ignorability) For all $u \geq 0$, we have

$$
P(T(1) \geq u | G = a, X) = P(T(1) \geq u | G = c, X),$$

$$
P(T(0) \geq u | G = c, X) = P(T(0) \geq u | G = n, X).$$

▶ assumes sufficient baseline information to capture characteristics influencing both the noncompliance behavior and the potential outcomes

▶ extension of Ding and Lu. (2016); Jiang et al. (2022) to causal survival analysis

▶ a stronger version: $G \perp T(z) | X$ for $z = 0, 1$

Both unverifiable from observed data and sensitivity analysis can help.
Possible working models

1. **Assignment mechanism:**

\[ M_{\pi}: \pi(X) = P(Z = 1|X), \text{ the propensity score (Rosenbaum and Rubin, 1983).} \]

- in ADAPTABLE, \( \pi(X) = 0.5 \) by randomization, but modeling this process may gain efficiency (Zeng et al, 2021; Li, Buchanan, Cole, 2022)

2. **Noncompliance:**

\[ M_{e}: e_g(X) = P(G = g|X) \text{ for } g \in \{a, c, n\} \text{ the principal scores (Ding and Lu, 2016).} \]

- define \( e_g = E[e_g(X)] \) as strata proportion
- by monotonicity, we have \( e_c(X) = p_1(X) - p_0(X), e_a(X) = p_0(X), \) and \( e_n(X) = 1 - p_1(X) \), where \( p_z(X) = P(S = 1|Z = z, X) \) is the observed probability for receiving the 325-mg dosage.

- Can fit logistic regressions to obtain \( \hat{\pi}(X) \) and \( \hat{p}_z(X) \).
3. **Censoring:**

\[ \mathcal{M}_C: \quad S^C_{zs}(u|X) = P(C \geq u|Z = z, S = s, X) \]

▷ survival function of the censoring time within observed cell \((Z = z, S = s)\).

4. **Survival outcome (of interest):**

\[ \mathcal{M}_T: \quad S_{zs}(u|X) = P(T \geq u|Z = z, S = s, X) \]

▷ survival function of the time-to-event outcome of interest within observed cell \((Z = z, S = s)\)

▷ Can fit Cox proportional hazards models to obtain \(\hat{S}^C_{zs}(u|X)\) and \(\hat{S}_{zs}(u|X)\)

▷ working models and no attempt to interpret HR as causal parameter
Moment estimators

- We do not need all models to point identify PSCEs

- We characterized 3 moment-type estimators of $\Delta_g(u)$, each depending on part of, but not all of, the 4 working models $M_\pi$, $M_e$, $M_C$, and $M_T$.

<table>
<thead>
<tr>
<th>$\Delta_g^{(1)}(u)$</th>
<th>$\Delta_g^{(2)}(u)$</th>
<th>$\Delta_g^{(3)}(u)$</th>
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</thead>
<tbody>
<tr>
<td>$\hat{\Delta}_g^{(1)}(u)$</td>
<td>$\hat{\Delta}_g^{(2)}(u)$</td>
<td>$\hat{\Delta}_g^{(3)}(u)$</td>
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<td>✓</td>
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<td>✓</td>
</tr>
</tbody>
</table>

- $\hat{\Delta}_g^{(1)}(u)$, $\hat{\Delta}_g^{(2)}(u)$, and $\hat{\Delta}_g^{(3)}(u)$ consistent to $\Delta_g(u)$ if $M_{\pi+e+C}$, $M_{e+T}$, and $M_{\pi+T}$ is correctly specified, respectively

- $M_{\alpha+b}$ is the intersection model, hence all 3 estimators are only singly robust
Combing multiple working models with complete data

- Ideal to leverage all working models to improve robustness and efficiency
- Suppose the true failure time can be observed (no censoring) with the complete data $\mathcal{A} = \{X, Z, S, T\}$.
- Adapted from Jiang et al. (2022)\(^4\), a multiply robust estimator of $S_{1,c}(u)$ can be obtained by solving the following estimating equation,

$$\mathbb{P}_n \left[ \psi_{1,c}^{mr} (\mathcal{A}) \right] = 0,$$

where

$$\psi_{1,c}^{mr} (\mathcal{A}) = \frac{e_c(X)}{\tilde{p}_1 - \tilde{p}_0} \frac{S}{p_1(X)} \frac{Z}{\pi(X)} \mathbb{I}(T \geq u) - S_{1,c}(u)$$

$$+ \frac{e_c(X)}{\tilde{p}_1 - \tilde{p}_0} \left( 1 - \frac{Z}{\pi(X)} \right) S_{11}(u|X)$$

$$+ \frac{S_{11}(u|X)}{\tilde{p}_1 - \tilde{p}_0} \left[ \frac{1 - Z}{1 - \pi(X)} (S - p_0(X)) + \frac{p_0(X)}{p_1(X)} \frac{Z}{\pi(X)} (p_1(X) - S) \right],$$

- The first row: a weighting-based estimating equation of $S_{1,c}(u)$; the last two rows: augmented zero-mean terms based on outcome modeling.

Accommodate right-censoring

- Observed data subject to censoring: \( \mathcal{O} = \{X, Z, S, U, \delta\} \)

- **Key idea:** identify a set of unbiased estimating functions that depend only on the observed data \( \mathcal{O} \):

\[
\psi_{1,c}(\mathcal{O}) = \frac{\delta \psi_{1,c}^{mr}(\mathcal{A})}{S_{ZS}^C(U|X)} + \int h(r, Z, S, X) dM_{ZS}^C(r|X),
\]

where \( h(t, Z, S, X) \) can be arbitrary function and \( dM_{ZS}^C(t|X) \) is the censoring process martingale (within in cell defined by \((Z, S))\).

- The resulting estimator is an *augmented inverse probability of weighted complete-case* (AIPWCC) estimator (Tsiatis, 2006)

- The optimal choice of \( h(t, Z, S, X) \) to maximize efficiency is

\[
h(t, Z, S, X) = \frac{\mathbb{E} \left[ \psi_{1,c}^{mr}(\mathcal{A}) | T \geq t, Z, S, X \right]}{S_{ZS}^C(t|X)}
\]
The proposed estimator

After some algebra, the proposed estimator has the following explicit form

\[
\hat{S}_{1,c}^{mr}(u) = \mathbb{P}_n \left\{ \frac{\hat{e}_c(X)}{\hat{p}_1 - \hat{p}_0} \frac{S}{\hat{p}_1(X)} \frac{Z}{\hat{\pi}(X)} \left[ \mathbb{I}(U \geq u) \frac{\hat{S}_{11}(u|X)}{\hat{S}_{11}(u|X)} + \hat{S}_{11}(u|X) \int_0^u \frac{d\hat{M}_{11}^C(r|X)}{\hat{S}_{11}(r|X)\hat{S}_{11}^C(r|X)} \right] \\
+ \frac{\hat{S}_{11}(u|X)}{\hat{p}_1 - \hat{p}_0} \left[ \frac{1 - Z}{1 - \hat{\pi}(X)} (S - \hat{p}_0(X)) + \frac{\hat{p}_0(X)}{\hat{p}_1(X)} \frac{Z}{\hat{\pi}(X)} (\hat{p}_1(X) - S) \right] \\
+ \frac{\hat{e}_c(X)}{\hat{p}_1 - \hat{p}_0} \left( 1 - \frac{Z}{\hat{\pi}(X)} \right) \hat{S}_{11}(u|X) \right\},
\]

where \( \mathbb{P}_n[V] = \frac{1}{n} \sum_{i=1}^n V_i \) is the empirical average operator.

Similar ideas to estimate counterfactual survival functions in other strata

Bootstrap variance
Multiple robustness

- **Result.** (Multiple robustness)

  Suppose that Assumptions 1–5 hold. For all $z \in \{0, 1\}$ and $g \in \{c, n, a\}$, $\mathcal{S}^{mr}_{z,g}(u)$ is consistent to $\mathcal{S}_{z,g}(u)$ under the union model $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$. As a consequence, $\mathcal{\hat{\Delta}}^{mr}_{g}(u)$ is also consistent to $\Delta_{g}(u)$ under $\mathcal{M}_{\pi+e+C} \cup \mathcal{M}_{\pi+T} \cup \mathcal{M}_{e+T}$ for all $g \in \{c, n, a\}$.

- **remark 1:** the result is general and can be applied to observational study (where modeling assignment $\mathcal{M}_{\pi}$ is necessary for removing confounding bias)

- **remark 2:** in ADAPTABLE, because $\mathcal{M}_{\pi}$ is known under randomization, $\mathcal{\hat{\Delta}}^{mr}_{g}(u)$ becomes a doubly robust estimator, in that consistency holds under the union model $\mathcal{M}_{e+C} \cup \mathcal{M}_{T}$
  
  - correct weighting or correct outcome modeling, but not necessarily both

  - simulations confirm the robustness property
Application to ADAPTABLE

- Working models (all models adjusting for all baseline characteristics)
  - $\mathcal{M}_\pi$: logistic regression
  - $\mathcal{M}_e$: logistic regression
  - $\mathcal{M}_C$: Cox regression
  - $\mathcal{M}_T$: Cox regression

- Proportion of each principal strata estimated from principal scores (Figure)

- For any $V \in X$, we calculate its estimated mean and variance within each strata

\[
\begin{align*}
\hat{\mathbb{E}}[V|G = g] &= \mathbb{P}_n \left[ \frac{\hat{e}_g(X)}{\hat{\epsilon}_g} V \right] \\
\hat{\text{Var}}[V|G = g] &= s_g^2 \text{ given by the principal score weighted variance}
\end{align*}
\]

- useful in describing and comparing demographic and clinical characteristics among different compliance strata.

Figure: The estimated proportions of each strata (i.e., $\hat{e}_g$)
Strata characteristics

- **Always low-dose:** older, higher prevalence of cardiovascular diseases and worse medical history, more 81-mg aspirin users

- **Compliers:** less non-internet users, more white patients

- **Always high-dose:** youngest, less medical conditions, more 325-mg aspirin users

Table 3: Mean and standard deviation of baseline characteristics among always low-dose takers, compliers, and always high-dose takers, ADAPTABLE trial, 2016–2020.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Always low-dose takers</th>
<th>Compliers</th>
<th>Always high-dose takers</th>
<th>Max ASD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.70 (9.34)</td>
<td>66.44 (9.36)</td>
<td>66.02 (9.56)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.32 (0.47)</td>
<td>0.29 (0.45)</td>
<td>0.28 (0.45)</td>
<td>0.09</td>
</tr>
<tr>
<td>White race</td>
<td>0.78 (0.41)</td>
<td>0.89 (0.31)</td>
<td>0.80 (0.40)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>0.04 (0.20)</td>
<td>0.03 (0.16)</td>
<td>0.04 (0.19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Non-internet users</td>
<td>0.21 (0.41)</td>
<td>0.09 (0.28)</td>
<td>0.24 (0.42)</td>
<td>0.41</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.10 (0.31)</td>
<td>0.08 (0.28)</td>
<td>0.14 (0.35)</td>
<td>0.18</td>
</tr>
<tr>
<td>P2Y12 inhibitor</td>
<td>0.25 (0.43)</td>
<td>0.22 (0.41)</td>
<td>0.22 (0.42)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Medical History**

- Myocardial infarction: 0.39 (0.49), 0.35 (0.48), 0.38 (0.49), 0.09
- Atrial fibrillation: 0.09 (0.28), 0.08 (0.27), 0.10 (0.30), 0.09
- Percutaneous coronary intervention: 0.46 (0.50), 0.40 (0.49), 0.39 (0.49), 0.15
- Coronary artery disease: 0.96 (0.19), 0.95 (0.21), 0.94 (0.24), 0.12
- Coronary-artery bypass grafting: 0.26 (0.44), 0.25 (0.43), 0.25 (0.43), 0.02
- Hypertension: 0.89 (0.32), 0.85 (0.35), 0.90 (0.30), 0.13
- Hyperlipidemia: 0.91 (0.28), 0.90 (0.30), 0.88 (0.32), 0.10
- Peripheral artery disease: 0.29 (0.45), 0.22 (0.41), 0.25 (0.44), 0.16
- Congestive heart failure: 0.27 (0.44), 0.22 (0.41), 0.26 (0.44), 0.12
- History of bleeding: 0.11 (0.31), 0.07 (0.26), 0.10 (0.30), 0.12

**Aspirin use before trial**

- Prior dose: 81 mg: 0.90 (0.30), 0.87 (0.34), 0.45 (0.50), 1.11
- Prior dose: 325 mg: 0.08 (0.27), 0.11 (0.32), 0.47 (0.50), 0.97

*Max ASD is the maximum pairwise absolute standardized difference across the three principal strata.
Balance check

- Why balance check? To empirically check evidence for principal score model adequacy

- Balance metrics: The *weighted standardized mean differences* (SMDs) of a given covariate $V$ across the four observed $(Z, S)$-strata, $(Z = 1, S = 1)$, $(Z = 0, S = 1)$, $(Z = 1, S = 0)$, and $(Z = 0, S = 0)$:

  \[
  \text{SMD}_c = \frac{1}{s_c} \left| \frac{\text{Pr}_n \left[ ZS W_{1,c}(X) V \right]}{\text{Pr}_n[ZS]} - \frac{(1 - Z)(1 - S) W_{0,c}(X) V}{\text{Pr}_n[(1 - Z)(1 - S)]} \right|
  \]

  \[
  \text{SMD}_n = \frac{1}{s_n} \left| \frac{Z(1 - S) W_{1,n}(X) V}{\text{Pr}_n[Z(1 - S)]} - \frac{(1 - Z)(1 - S) W_{0,n}(X) V}{\text{Pr}_n[(1 - Z)(1 - S)]} \right|
  \]

  \[
  \text{SMD}_a = \frac{1}{s_a} \left| \frac{ZS W_{1,a}(X) V}{\text{Pr}_n[ZS]} - \frac{(1 - Z)S W_{0,a}(X) V}{\text{Pr}_n[(1 - Z)S]} \right|
  \]

  where $W_{z,g}(X)$ for $z \in \{0, 1\}$ and $g \in \{c, a, n\}$ are specified weights.

- When $W_{z,g}(X) = 1$, the SMDs measure the systematic difference of $X$ across different $(Z, S)$-strata, and therefore reflects heterogeneity of $X$ due to patients’ noncompliance behavior

- When $W_{z,g}(X)$ is set to the (true) principal score weight, SMDs should be 0
Balance check - cont’d

Figure: Balance check for baseline characteristics. The red ‘●’ symbol indicates the unweighted SMDs and the blue ‘▲’ symbol indicates the weighted SMDs by the principal score weighting.
Implement the proposed estimator of the PSCEs among the always low-dose, compliers, and always high-dose.

**Figure:** The principal survival causal effects (PSCEs) and the principal survival probability curves.
Sensitivity analysis for principal ignorability (PI)

- PI holds if there is no residual confounding between $G$ and $T$ conditional on $X$
- PI violated if there exists unmeasured confounding ($U$) between $G$ and $T$
- One potential $U$: digestive disease, which may increase the risk of death. Moreover, people with digestive diseases may prefer not to take high aspirin dosage due to its risk on bleeding.

- Consider sensitivity functions to measure departure from PI:

\[
\varepsilon_1(t, X) = \frac{\mathbb{P}(T(1) \geq t | G = c, X)}{\mathbb{P}(T(1) \geq t | G = a, X)} = \exp \left\{ \xi_1 \times \left( \frac{t}{t_{\text{max}}} \right) \right\}
\]

\[
\varepsilon_0(t, X) = \frac{\mathbb{P}(T(0) \geq t | G = c, X)}{\mathbb{P}(T(0) \geq t | G = n, X)} = \exp \left\{ \xi_0 \times \left( \frac{t}{t_{\text{max}}} \right) \right\},
\]

- We use $\{\xi_1, \xi_0\}$ to control the pattern of the two sensitivity functions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>$\xi_1$</th>
<th>$\xi_0$</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benchmark</td>
<td>0</td>
<td>0</td>
<td>PI holds</td>
</tr>
<tr>
<td>I</td>
<td>–</td>
<td>+</td>
<td>always low-dose takers &lt; compliers &lt; always high-dose takers</td>
</tr>
<tr>
<td>II</td>
<td>+</td>
<td>–</td>
<td>always high-dose &lt; compliers &lt; always low-dose takers</td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>–</td>
<td>compliers &lt; {always high-dose, always low-dose takers}</td>
</tr>
<tr>
<td>IV</td>
<td>+</td>
<td>+</td>
<td>{always high-dose, always low-dose takers} &lt; compliers</td>
</tr>
</tbody>
</table>

Note: ‘A<B’ means that A is less healthier than B due to unobserved confounders (i.e., $U$).
Choice of sensitivity parameter

▶ For fixed \{\xi_1, \xi_0\}, we develop a bias-corrected estimator for PSCE, \(\hat{\Delta}_g^{bc}(u)\), which is consistent under \(M_{\pi+e+C} \cup M_{\pi+T}\).

▶ Under randomization, doubly robust \((M_{e+C} \cup M_T)\)

▶ A plausible scenario: always low-dose takers often less healthier than compilers; always high-dose taker often the healthiest.

▶ We choose \(\xi_1 \in [\log(0.9), 0]\) and \(\xi_0 \in [0, \log(1.1)]\), corresponding to Scenario I in previous table

▶ since \(\xi_1\) and \(\xi_0\) defined based on conditional causal survival function, there is a bound on these values

▶ a simple choice but can extend to \(\xi_1(X)\) and \(\xi_0(X)\)
Sensitivity analysis: results

PI holds \((\xi_1, \xi_2) = (\log 0.95, 0)\)

Principal survival causal effects

Always low-dose takers

Compliers

Always high-dose takers

Principal survival causal effects

time
Discussion

▶ Carried out sensitivity analysis for monotonicity (A4) – results robust to this assumption in ADAPTABLE (back-up slides)

▶ Some conclusions under PI:
  ▶ (1) always high-dose takers appear to benefit
  ▶ (2) compliers slightly benefit
  ▶ (3) always low-dose takers appear not to benefit

▶ (2) and (3) may change if PI does not hold (depending on how rich the collected baseline covariates are)
  ▶ mechanisms of these effects require further studies

▶ Limitations:
  ▶ composite outcomes
  ▶ complete case analysis without addressing treatment discontinuation
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References - cont’d


Simulation study (ignorable assignment)

- **Scenario 1–4**: the union model $M_{\pi+e+C} \cup M_{\pi+T} \cup M_{e+T}$ is correctly specified.
- **Scenario 5**: all models are misspecified.

| Table 1: Simulation results of $\hat{S}_{0,c}(u)$, where $M_e, M_\pi, M_T$, and $M_C$ indicate whether the working model for principal score, propensity score, time-to-event and time-to-censoring is correctly specified (denoted by a 'T' label) or misspecified (denoted by a 'F' label). |
|-----------------|---------------|---------------|-------------|---------------|-----------------|
| **Scenario 1**  | **u** | $S_{0,c}(u)$ | $\hat{S}_{0,c}(u)$ | **Bias** | **Monte Carlo SE** | **Coverage Rate** |
| $M_e$ T          | 1   | 0.695         | 0.695          | 0.000     | 0.050           | 0.946           |
| $M_\pi$ T        | 2   | 0.517         | 0.518          | 0.000     | 0.048           | 0.960           |
| $M_T$ T          | 3   | 0.397         | 0.395          | -0.002    | 0.046           | 0.960           |
| $M_C$ T          | 4   | 0.309         | 0.306          | -0.003    | 0.039           | 0.968           |
| $M_C$ T          | 5   | 0.245         | 0.242          | -0.003    | 0.036           | 0.964           |
| **Scenario 2**  | **u** | $S_{0,c}(u)$ | $\hat{S}_{0,c}(u)$ | **Bias** | **Monte Carlo SE** | **Coverage Rate** |
| $M_e$ T          | 1   | 0.695         | 0.693          | -0.002    | 0.048           | 0.960           |
| $M_\pi$ T        | 2   | 0.517         | 0.517          | 0.000     | 0.048           | 0.972           |
| $M_T$ F          | 3   | 0.397         | 0.394          | -0.002    | 0.046           | 0.970           |
| $M_C$ T          | 4   | 0.309         | 0.307          | -0.003    | 0.041           | 0.960           |
| $M_C$ T          | 5   | 0.245         | 0.243          | -0.002    | 0.037           | 0.970           |
| **Scenario 3**  | **u** | $S_{0,c}(u)$ | $\hat{S}_{0,c}(u)$ | **Bias** | **Monte Carlo SE** | **Coverage Rate** |
| $M_e$ F          | 1   | 0.695         | 0.693          | -0.002    | 0.172           | 0.936           |
| $M_\pi$ T        | 2   | 0.517         | 0.517          | -0.001    | 0.133           | 0.946           |
| $M_T$ T          | 3   | 0.397         | 0.394          | -0.003    | 0.108           | 0.956           |
| $M_C$ F          | 4   | 0.309         | 0.306          | -0.004    | 0.084           | 0.966           |
| $M_C$ F          | 5   | 0.245         | 0.241          | -0.003    | 0.068           | 0.960           |
| **Scenario 4**  | **u** | $S_{0,c}(u)$ | $\hat{S}_{0,c}(u)$ | **Bias** | **Monte Carlo SE** | **Coverage Rate** |
| $M_e$ T          | 1   | 0.695         | 0.692          | -0.003    | 0.042           | 0.962           |
| $M_\pi$ F        | 2   | 0.517         | 0.517          | 0.000     | 0.044           | 0.962           |
| $M_T$ T          | 3   | 0.397         | 0.395          | -0.002    | 0.043           | 0.962           |
| $M_C$ F          | 4   | 0.309         | 0.308          | -0.002    | 0.038           | 0.968           |
| $M_C$ F          | 5   | 0.245         | 0.244          | -0.001    | 0.035           | 0.976           |
| **Scenario 5**  | **u** | $S_{0,c}(u)$ | $\hat{S}_{0,c}(u)$ | **Bias** | **Monte Carlo SE** | **Coverage Rate** |
| $M_e$ F          | 1   | 0.695         | 0.761          | 0.066     | 0.024           | 0.246           |
| $M_\pi$ F        | 2   | 0.517         | 0.600          | 0.083     | 0.029           | 0.228           |
| $M_T$ F          | 3   | 0.397         | 0.479          | 0.082     | 0.029           | 0.234           |
| $M_C$ F          | 4   | 0.309         | 0.387          | 0.078     | 0.029           | 0.264           |
| $M_C$ F          | 5   | 0.245         | 0.318          | 0.073     | 0.029           | 0.328           |
# Back-up: Baseline table

- **Balance check for baseline characteristics in each treatment arm**

Table 2: Mean and standard deviation of baseline characteristics stratified by the treatment assignment group, ADAPTABLE trial, 2016–2020.

<table>
<thead>
<tr>
<th>Variable</th>
<th>81-mg Group (N = 5239)</th>
<th>325-mg Group (N = 4791)</th>
<th>ASD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.00 (9.45)</td>
<td>66.77 (9.32)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.29 (0.46)</td>
<td>0.31 (0.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>White race</td>
<td>0.84 (0.37)</td>
<td>0.85 (0.36)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>0.03 (0.18)</td>
<td>0.03 (0.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-internet users</td>
<td>0.15 (0.35)</td>
<td>0.14 (0.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.09 (0.29)</td>
<td>0.10 (0.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>P2Y12 inhibitor</td>
<td>0.23 (0.42)</td>
<td>0.23 (0.42)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.37 (0.48)</td>
<td>0.36 (0.48)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.08 (0.27)</td>
<td>0.09 (0.28)</td>
<td>0.03</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>0.42 (0.49)</td>
<td>0.42 (0.49)</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.95 (0.21)</td>
<td>0.96 (0.20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary-artery bypass grafting</td>
<td>0.25 (0.44)</td>
<td>0.25 (0.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.87 (0.34)</td>
<td>0.87 (0.33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.90 (0.30)</td>
<td>0.91 (0.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0.24 (0.43)</td>
<td>0.25 (0.44)</td>
<td>0.03</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.23 (0.42)</td>
<td>0.25 (0.43)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>0.08 (0.28)</td>
<td>0.09 (0.29)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Aspirin use before trial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior dose: 81 mg</td>
<td>0.85 (0.36)</td>
<td>0.86 (0.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior dose: 325 mg</td>
<td>0.12 (0.33)</td>
<td>0.12 (0.33)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*ASD: the absolute standardized difference.
If monotonicity does not hold, defiers exist and we have four strata \( G \in \{c, n, a, d\} \).

The following sensitivity parameter captures the deviation from monotonicity:

\[
\zeta = \frac{\Pr(G = d|X)}{\Pr(G = c|X)},
\]

—ratio between the probability of defiers and compliers given \( X \).

\( \zeta \) takes values from 0 to \( \infty \), and monotonicity holds with \( \zeta = 0 \).

If we further assume that the treatment assignment has a positive effect on the treatment receipt (i.e., \( \mathbb{E}[S(1) - S(0)] \geq 0 \)), then \( \zeta \) is bounded by

\[
0 \leq \zeta \leq 1 - \frac{p_1 - p_0}{\min(p_1, 1 - p_0)},
\]

where \( p_z = \mathbb{E}[p_z(X)] \).

In ADAPTABLE, the estimated bound is \( \zeta \in [0, 0.103] \).

For a fixed value \( \zeta \), we developed a modified estimator, which is consistent under \( M_{\pi+e+C} \cup M_{\pi+T} \cup M_{e+T} \) for any \( g \in \{c, n, a, d\} \).
Back-up: Sensitivity for monotonicity