# Treatment effect estimation for time-to-event endpoints with intercurrent events

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# Outline

# Intercurrent Events

- The International Conference on Harmonization (ICH) E9 (R1) addendum on *Estimands and sensitivity analysis in clinical trials* to the guideline on *Statistical principles for clinical trials* (ICH, 2019).
- Intercurrent events refer to the events "occurring after treatment initiation that affect either the interpretation of or the existence of the measurements associated with the clinical question of interest".
- Two types of intercurrent events:
  1. Semi-competing risks – modifying the hazard of primary outcome event.
  2. Competing risks – preventing the primary outcome event from happening.

# ICH E9 (R1)

- Five strategies to address intercurrent events: treatment policy strategy, composite variable strategy, hypothetical strategy, while on treatment strategy, and principal stratum strategy.
- ICH E9 (R1) was proposed in the context of randomized controlled trials (RCTs), but the insights can be extended to observational studies.

# Notations

- Consider a randomized controlled trial (RCT) with $n$ individuals.
- $W$: binary treatment.
- $T(w)$: potential time to primary outcome event (if any).
- $R(w)$: potential time to intercurent event (if any).
- An upper limit for the monitoring time since treatment initiation is set to be $t^*$.
- If primary outcome events are prevented by intercurrent events, denote $T(w) = \infty$.
- If no intercurrent events happen before the end of follow-up, denote $R(w) = \infty$.

# Forms of Estimands

- In general, a treatment effect is defined as the contrast of

$$\text{Summary}\{\text{Outcome}(\text{Treatment}) \mid \text{Population}\}.$$

- We use $\mu_w^k(t)$ to denote the cumulative incidence function (CIF) of the primary outcome event under treatment condition $w$ and strategy $k$.
- Treatment effect

$$\tau^k(t) = \mu_1^k(t) - \mu_0^k(t).$$

# Treatment Policy Strategy

- The treatment policy strategy addresses intercurrent events by expanding the initial treatment conditions to a treatment policy (intention-to-treat).
- Treatment policy: the assignment of test/control drug plus the occurrence of intercurrents as natural.
- This strategy is valid only if primary outcome events cannot be prevented by intercurrent events.

$$\begin{aligned}\tau^{\text{tp}}(t) &:= \mu_1^{\text{tp}}(t) - \mu_0^{\text{tp}}(t) \\ &:= P(T(1, R(1)) < t) - P(T(0, R(0)) < t) \\ &= P(T(1) < t) - P(T(0) < t).\end{aligned}$$

# Composite Variable Strategy

- The composite variable strategy addresses intercurrent events by expanding the outcome variables. It aggregates the intercurrent events and primary outcome variable as one composite outcome variable.
- The idea is not new in the notion of progression-free survival.
- One widely used composite outcome variable is the first occurrence $R(w) \wedge T(w) = \min\{T(w), R(w)\}$.

$$\begin{aligned}\tau^{\text{cv}}(t) &:= \mu_1^{\text{cv}}(t) - \mu_0^{\text{cv}}(t) \\ &:= P(R(1) \wedge T(1) < t) - P(R(0) \wedge T(0) < t).\end{aligned}$$

- Other form: quality-adjusted lifetime.

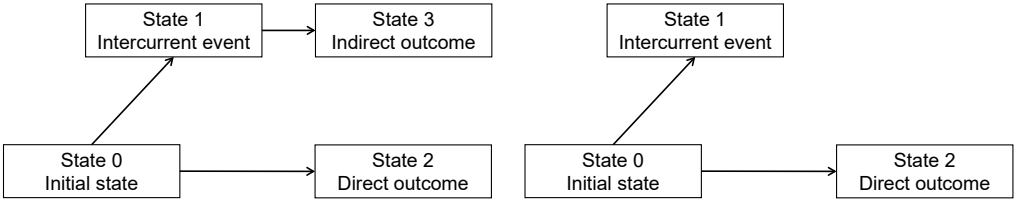
# While On Treatment Strategy

- The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events.
- The failures of primary outcome events should not be counted in the cumulative incidence if intercurrent events occurred.

$$\begin{aligned}\tau^{\text{wo}}(t) &:= \mu_1^{\text{wo}}(t) - \mu_0^{\text{wo}}(t) \\ &:= P(T(1) < t, R(1) \geq t) - P(T(0) < t, R(0) \geq t).\end{aligned}$$

- The $\mu_w^{\text{wo}}(t)$ is also known as cause-specific cumulative incidence or subdistribution function in the competing risks model.

# The Above Three Strategies under Multi-State Models




| | Semi-competing risks | Competing risks |
|---|---|---|
| Treatment policy strategy | $F_2(t) + F_3(t)$ | – |
| Composite variable strategy | $F_1(t) + F_2(t)$ | $F_1(t) + F_2(t)$ |
| While on treatment strategy | $F_2(t)$ | $F_2(t)$ |

# Hypothetical Strategy

- The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways.
- We use $T'(w)$ to denote the time to the primary outcome event in the hypothetical scenario.

$$\begin{aligned}\tau^{\text{hp}}(t) &:= \mu_1^{\text{hp}}(t) - \mu_0^{\text{hp}}(t) \\ &:= P(T'(1) < t) - P(T'(0) < t).\end{aligned}$$

- How to envision the hypothetical scenario?

# Hypothetical Strategy

- To manipulate the hazard specific to intercurrent events

$$d\Lambda_2(t; w) := P(t \leq R(w) < t + dt \mid T(w) \geq t, R(w) \geq t),$$

  while assuming the hazard specific to primary outcome events

$$d\Lambda_1(t; r, w) := P(t \leq T(w) < t + dt \mid T(w) \geq t, I\{R(w) \leq t\} = r)$$

  is unchanged.
- Let $d\Lambda_2'(t; w)$ and $d\Lambda_1'(t; r, w)$ be the hazards specific to intercurrent events and primary outcome events in the hypothetical scenario respectively, with $d\Lambda_1'(t; r, w) = d\Lambda_1(t; r, w)$, $w = 1, 0$.

# Hypothetical Strategy: Scenario I

- The intercurrent events when individuals were assigned to test drugs were only permitted if such intercurrent events would have occurred if these individuals were assigned to placebo,

$$d\Lambda_2'(t;0) = d\Lambda_2'(t;1) = d\Lambda_2(t;0).$$

- This strategy is related to the natural effects.
- Sequential ignorability is required for mediation interpretation – no confounding between the primary outcome event and intercurrent events.

# Hypothetical Strategy: Scenario II

- The intercurrent events are absent in the hypothetical scenario for all individuals,

$$d\Lambda_2'(t;0) = d\Lambda_2'(t;1) = 0.$$

- This hypothetical scenario leads to an estimand called the marginal cumulative incidence.
- This strategy is related to the controlled effects.
- Sequential ignorability is required for mediation interpretation – no confounding between the primary outcome event and intercurrent events.

# Principal Stratum Strategy

- The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$.
- We are interested in a principal stratum comprised of individuals who would never experience intercurrent events regardless of receiving which treatment $\{R(1) = R(0) = \infty\}$.

$$\begin{aligned}\tau^{\text{ps}}(t) &:= \mu_1^{\text{ps}}(t) - \mu_0^{\text{ps}}(t) \\ &:= P(T(1) < t \mid R(1) = R(0) = \infty) - P(T(0) < t \mid R(1) = R(0) = \infty).\end{aligned}$$

- The target population is impossible to identify. Principal ignorability is required.

# Treatment Policy Strategy: Identification

- To apply this strategy, we need data $(\tilde{T}, \Delta^T, W)$.
- The hazard function of the potential primary outcome event

$$\begin{aligned} d\Lambda(t; w) &:= P(t \leq T(w) < t + dt \mid T(w) \geq t) \\ &= P(t \leq \tilde{T} < t + dt, \Delta^T = 1 \mid \tilde{T} \geq t, W = w). \end{aligned}$$

- Next, we can identify $\tau^{\text{tp}}(t)$ from

$$\mu_w^{\text{tp}}(t) = 1 - \exp\{-\Lambda(t; w)\}.$$

# Composite Variable Strategy: Identification

- To estimate this quantity, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T \vee \Delta^R, W)$.
- The hazard function of the composite outcome variable $T(w) \wedge R(w)$

$$\begin{aligned} d\Lambda_{12}(t; w) &:= P(t \leq T(w) \wedge R(w) < t + dt \mid T(w) \wedge R(w) \geq t) \\ &= P(t \leq \tilde{T} \wedge \tilde{R} < t + dt, \Delta^T \vee \Delta^R = 1 \mid \tilde{T} \wedge \tilde{R} \geq t, W = w). \end{aligned}$$

- Next, $\tau^{\text{cv}}(t)$ is identified from

$$\mu_w^{\text{cv}}(t) = 1 - \exp\{-\Lambda_{12}(t; w)\}.$$

# While On Treatment Strategy: Identification

- To estimate these quantities, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- The hazard functions specific to primary outcome events and intercurrent events

$$d\Lambda_1(t; w) = P(t \leq \tilde{T} < t + dt, \Delta^T = 1 \mid \tilde{T} \geq t, \tilde{R} \geq t, W = w),$$
$$d\Lambda_2(t; w) = P(t \leq \tilde{R} < t + dt, \Delta^R = 1 \mid \tilde{T} \geq t, \tilde{R} \geq t, W = w).$$

- In fact,

$$d\Lambda_1(t; w) + d\Lambda_2(t; w) = d\Lambda_{12}(t; w).$$

- Next, $\tau^{\text{wo}}(t)$ is identified from

$$\mu_w^{\text{wo}}(t) = \int_0^t \exp\{-\Lambda_1(s; w) - \Lambda_2(s; w)\} d\Lambda_1(s; w).$$

# Hypothetical Strategy I: Identification

- For competing risks data, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- The estimand of hypothetical scenario I is identified from

$$\mu_w^{\text{hs,I}}(t) = \int_0^t \exp\{-\Lambda_1(s; w) - \Lambda_2(s; 0)\} d\Lambda_1(s; w).$$

- For semi-competing risks data, we need data $(\tilde{T}, \tilde{R}, \Delta^T, \Delta^R, W)$.
- The estimand of hypothetical scenario I is identified from

$$\begin{aligned}\mu_w^{\text{hs,I}}(t) = 1 &- \exp\{-\Lambda_1(t; 0, w) - \Lambda_2(t; 0)\} \\ &- \int_0^t \exp\{-\Lambda_1(s; 0, w) - \Lambda_2(s; 0) - \Lambda_1(t; 1, w) + \Lambda_1(s; 1, w)\} d\Lambda_2(s; 0).\end{aligned}$$

# Hypothetical Strategy II: Identification

- To estimate this quantity, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T(1-\Delta^R), W)$.
- The estimand of hypothetical scenario II can be identified from

$$\mu_w^{\text{hs,II}}(t) = 1 - \exp\{-\Lambda_1(t; w)\}.$$

- Of note, $\tau^{\text{hs,II}}(t)$ evaluates the contrast of the marginal distributions of $T(1)$ and $T(0)$ with intercurrent events viewed as independent censoring.

# Principal Stratum Strategy: Identification

- To estimate this quantity, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- Principal ignorability: $T(w)$ can be correlated with $R(w)$ but should not have cross-world reliance on $R(1-w)$.
- The estimand can be identified from

$$\begin{aligned}
\mu_w^{\mathsf{ps}}(t) &= P(T(w) < t \mid R(1) = \infty, R(0) = \infty) \\
&= P(T(w) < t \mid R(w) = \infty) \\
&= P(T(w) < t \mid R(w) \geq t^*) \\
&= \frac{\int_0^t \exp\{-\Lambda_{12}(s; w)\} d\Lambda_1(s; w)}{1 - \int_0^{t^*} \exp\{-\Lambda_{12}(s; w)\} d\Lambda_2(s; w)}.
\end{aligned}$$

# Artificial Example

- Suppose that the hazard specific to the potential primary outcome event is $\lambda_1(t; w) = a_w t$.
- Suppose that the hazard specific to the intercurrent event is $\lambda_2(t; w) = c_w$.
- Suppose the intercurrent event would neither prevent nor modify the hazard of the primary outcome event.
- Therefore, the marginal distribution of the potential primary outcome event $T(w) \sim \mathit{Weibull}(2, \sqrt{2/a_w})$.

# Artificial Example: CIF Under Competing Risks

| $k$ | Cumulative incidence $\mu_w^k(t)$, $0 \le t \le t^*$ |
|---|---|
| tp | Not applicable |
| cv | $1 - e^{-a_w t^2/2 - c_w t}$ |
| wo | $1 - e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t + c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}$ |
| hp,I | $1 - e^{-a_w t^2/2 - c_0 t} - e^{c_0^2/2a_w}(2\pi c_0^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t + c_0/a_w)) - \Phi(c_0/a_w^{1/2})\}$ |
| hp,II | $1 - e^{-a_w t^2/2}$ |
| ps | $\frac{1-e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t+c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}}{1-e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t^*+c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}}$ |

# Artificial Example: CIF Under Semi-Competing Risks

| $k$ | Cumulative incidence $\mu_w^k(t)$, $0 \le t \le t^*$ |
|---|---|
| tp | $1 - e^{-a_w t^2/2}$ |
| cv | $1 - e^{-a_w t^2/2 - c_w t}$ |
| wo | $1 - e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t + c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}$ |
| hp,I | $1 - e^{-a_w t^2/2}$ |
| hp,II | $1 - e^{-a_w t^2/2}$ |
| ps | $\frac{1-e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t+c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}}{1-e^{c_w^2/2a_w}(2\pi c_w^2/a_w)^{1/2}\{\Phi(a_w^{1/2}(t^*+c_w/a_w)) - \Phi(c_w/a_w^{1/2})\}}$ |

# Two Approaches for Observational Studies

- Baseline covariates $X$ should be adjusted for.
- Inverse probability weighting.
  — Weight the event-counting and at-risk processes by the inverse of treatment probability.
  — The uncertainty of the estimated propensity score is usually not accounted for.
- Semiparametrically efficient estimation.
  — Solve the estimating equation of the empirical efficient influence function.
  — Double robustness; Standard error based on the influence function; Test based on the restricted mean survival time lost.

# Summary: How to Address Intercurrent Events in Practice

- Data structure:
  — Competing risks, semi-competing risks.
- Strategy:
  — Treatment policy, composite variable strategy, while on treatment strategy, hypothetical strategy (I, II), principal stratum strategy.
- Estimation method:
  — Nonparametric estimation, inverse probability weighting, semiparametrically efficient estimation.
- Presentation:
  — Cumulative incidence function, treatment effect, $P$-value.

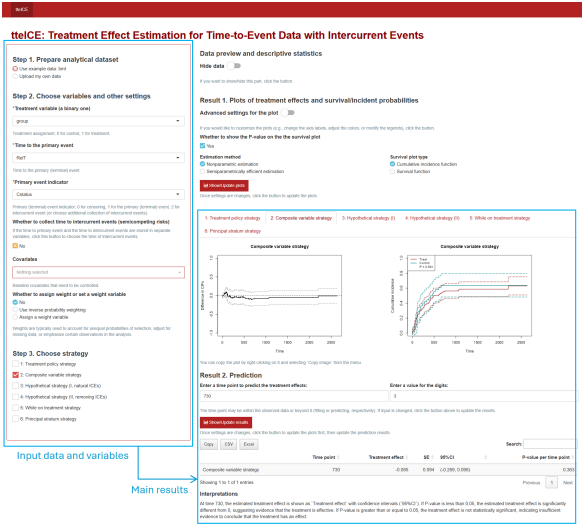
# Main Functions in the Package tteICE

| Function | Description |
|---|---|
| Main functions | |
| `scr.tteICE` | Use vector and matrix data to fit CIFs for semicompeting risks time-to-event data with intercurrent events |
| `surv.tteICE` | Use vector and matrix data to fit CIFs for competing risks time-to-event data with intercurrent events. |
| `tteICE` | Use formula to fit CIFs for time-to-event data with intercurrent events, either competing risks or semicompeting risks |
| `tteICEShiny` | Shiny app for tteICE |
| Results output functions (associated methods for "tteICE" objects) | |
| `bshaz.tteICE` | Extract baseline hazards of 'tteICE' objects |
| `coef.tteICE` | Extract coefficients of covariates in Cox models |
| `plot.tteICE` | Plot CIFs and treatment effects |
| `predict.tteICE` | Predict CIFs and treatment effects at specific time points |
| `print.tteICE` | Print a short summary of results from 'tteICE' objects |
| `print.summary.tteICE` | Print the summary |
| `summary.tteICE` | Summarize results from 'tteICE' objects |
| `zph.tteICE` | Check proportional hazards assumption of the Cox models |

# Formula and Methods in R

```
R> fit = tteICE(Surv(t1, d1) ~ A | z1 + z3 + z5, add.scr = ~ Surv(t2, d2),
R>              data = bmt, strategy = "treatment", method = "eff")
R>
R> print(fit, digits = 3)
# Input:
# tteICE(formula = Surv(t1, d1) ~ A | z1 + z3 + z5, add.scr = ~Surv(t2,
#     d2), data = bmt, strategy = "treatment", method = "eff")
# ------------------------------------------------------------------------
# Data type: semicompeting risks
# Strategy: treatment policy strategy
# Estimation method: semiparametrically efficient estimation
# Observations: 137 (including 99 treated and 38 control)
# Maximum follow-up time: 2640
# P-value of the average treatment effect: 0.064
```

# Rshiny App


tteICE
tteICE: Treatment Effect Estimation for Time-to-Event Data with Intercurrent Events
Step 1. Prepare analytical dataset
Use example data: bmt
Upload my own data
Step 2. Choose variables and other settings
*Treatment variable (a binary one)
group
Treatment assignment; 0 for control, 1 for treatment.
*Time to the primary event
ftpfl
Time to the primary (terminal) event.
*Primary event indicator
Dataset
Primary (terminal) event indicator; 0 for censoring, 1 for the primary (terminal) event, 2 for intercurrent event (or choose additional collection of intercurrent events).
Whether to collect time to intercurrent events (semicompeting risks)
If the time to primary event and the time to intercurrent events are stored in separate variables, click this button to choose the time of intercurrent events.
No
Covariates
Nothing selected
Baseline covariates that need to be controlled.
Whether to assign weight or set a weight variable
No
Use inverse probability weighting
Assign a weight variable
Weights are typically used to account for unequal probabilities of selection, adjust for missing data, or emphasize certain observations in the analysis.
Step 3. Choose strategy
1: Treatment policy strategy
2: Composite variable strategy
3: Hypothetical strategy (I; natural ICEs)
4: Hypothetical strategy (II; removing ICEs)
5: While on treatment strategy
6: Principal stratum strategy
Input data and variables
Data preview and descriptive statistics
Hide data
If you want to show/hide this part, click the button.
Result 1. Plots of treatment effects and survival/incident probabilities
Advanced settings for the plot
If you would like to customize the plots (e.g., change the axis labels, adjust the colors, or modify the legends), click the button.
Whether to show the P-value on the the survival plot
Yes
Estimation method
Nonparametric estimation
Semiparametrically-efficient estimation
Survival plot type
Cumulative incidence function
Survival function
Set (Re)edit plots
Once settings are changed, click the button to update the plots.
1: Treatment policy strategy
2: Composite variable strategy
3: Hypothetical strategy (I)
4: Hypothetical strategy (II)
5: While on treatment strategy
6: Principal stratum strategy
Composite variable strategy
Difference in CIFs
Time
Composite variable strategy
Trt=0
Trt=1
P = 0.763
Cumulative incidence
Time
You can copy the plot by right-clicking on it and selecting "Copy image" from the menu.
Result 2. Prediction
Enter a time point to predict the treatment effects:
730
Enter a value for the digits:
3
The time point may be within the observed data or beyond it (filling or predicting, respectively). If input is changed, click the button above to update the results.
Set (Re)edit results
Once settings are changed, click the button to update the plots first; then update the prediction results.
Copy
CSV
Excel
Search:
Time point
Treatment effect
SE
95%CI
P-value per time point
Composite variable strategy
730
-0.008
0.004
(-0.289, 0.066)
0.363
Showing 1 to 1 of 1 entries
Previous
1
Next
Interpretations
At time 730, the estimated treatment effect is shown as "Treatment effect" with confidence intervals ("95%CI"). If P-value is less than 0.05, the estimated treatment effect is significantly different from 0, suggesting evidence that the treatment is effective. If P-value is greater than or equal to 0.05, the treatment effect is not statistically significant, indicating insufficient evidence to conclude that the treatment has an effect.
Main results

# Welcom for discussion!

I have no current or past relationships with commercial entities.

Methodology papers:

[1] Deng, Y., Wang, Y., & Zhou, X. H. (2024). Direct and indirect treatment effects in the presence of semicompeting risks. *Biometrics*, 80(2), ujae032.
[2] Deng, Y., & Wang, R. (2025). Adjusted Nelson–Aalen estimators by inverse treatment probability weighting with an estimated propensity score. *Statistics in Medicine*, 44(10-12), e70085.
[3] Deng, Y., Han, S., & Zhou, X. H. (2025). Inference for cumulative incidences and treatment effects in randomized controlled trials with time-to-event outcomes under ICH E9 (R1). *Statistics in Medicine*, 44(10-12), e70091.