Tumor Burden–Integrated Estimands for Cancer Clinical Studies

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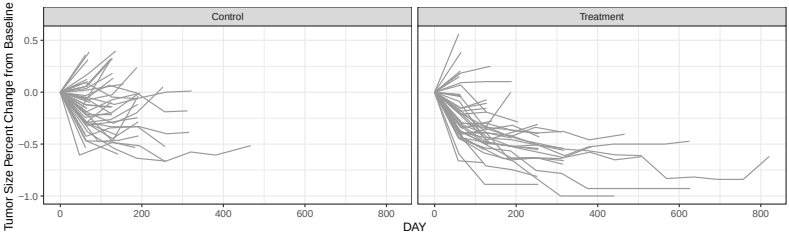
Background

Motivation example i

- Consider an oncology trial
- For each patient, tumor burden is scheduled to be observed at post-treatment visits
- Survival outcome, including time to disease progress and time to deaths, are also observed

Motivation example ii



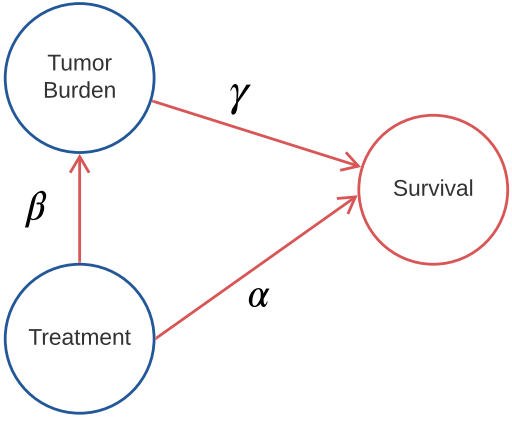
Motivation example iii

- Tumor burden affects various immune features in the tumor microenvironment
- Recognized as an important negative correlate of therapy-induced immune responses
- Typically, a tumor burden curve is summarized by the "best value" and integrated into the RECIST evaluation

Research question

Can we develop new methods to efficiently leverage tumor burden data in treatment evaluation?

A causal diagram



Existing methods i

- There is a substantial statistics literature on evaluating treatment effects based on the joint analysis of survival data and longitudinal outcomes such as tumor burden

Existing methods ii

- One major category of the existing methods aims to evaluate whether the longitudinal outcome can serve as a surrogate marker for survival and potentially replace it for treatment effect evaluation in early phase studies
- In such a case, one may need to demonstrate that $\alpha = 0$, $\beta \neq 0$ and $\gamma \neq 0$

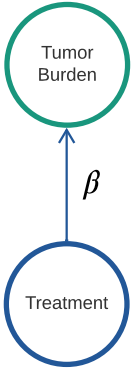
Existing methods iii

- Another category of the existing methods leverages the longitudinal outcome as a mediator for evaluating the treatment effect on survival
- By explicitly modeling the longitudinal and survival processes, these methods quantify the direct treatment effect on survival, β, and indirect treatment effect on survival through the longitudinal process, approximately $\beta \times \gamma$
- The goal is to evaluate the treatment effect on survival more efficiently

Existing methods iv

- Because of model complexity, most of the existing methods necessitate a substantial amount of data to be implemented; thus, they are more suitable for large-scale, late-phase studies
- In return, the methods aim to provide a comprehensive understanding of the underlying biological mechanisms through parameters α, β and γ, base on which the benefit and risk profile of the investigational treatment can be established

An alternative diagram i



An alternative diagram ii

- Focuses primarily on the treatment effect on the biological mechanism of *tumor growth*

Leveraging estimand thinking

- Intercurrent event
  - progression and death
- Composite strategy
  - "An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable"
- Hypothetical strategy
  - "The value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined"

Proposal I

- Address the clinical question of "what is the overall treatment effect on tumor burden and survival?"
- Develop an estimand based on the composite variable strategy
- We consider evaluating treatment effect based on tumor burden and survival, i.e., *the totality of the information*
- We *do not* set the goal to understand α, β and γ individually
- Instead, we propose to evaluate the *total treatment effect* (approximately) $\mathcal{E} = \alpha + \beta\gamma$

Proposal II

- Address the clinical question of "what is the treatment effect on tumor burden?"
- Develop an estimand based on the hypothetical strategy

The new estimands

Notation i

For patient i ($i = 1, \dots, N$),

- let $A_i = 1$ or 0 if the patient is assigned to the treatment or control arm respectively
- let X_i be the baseline covariates
- let Y_{ij} be the tumor burden measurement from baseline observed at t_{ij} ($j = 0, \dots, n_i$), where $t_{i,0} = 0$ corresponds to the baseline measurement time at randomization
- let $m_i(t)$ be the true tumor burden measurement without measurement error. That is,

$$Y_{ij} = m_i(t_{ij}) + \epsilon_{ij}$$

where ϵ_{ij} is a random error with mean 0

Notation ii

- let T_i denote time to disease progression or death, whichever is earlier
- let C_i denote time to censoring and δ_i the censoring indicator
- let $S_i = (\delta_i T_i, (1 - \delta_i) C_i, \delta_i)$
- let L_i be the time from randomization to the analysis (e.g., when the study finishes)

Notation iii

- In summary, the complete data of patient i is

$$\mathcal{D}_i = \{X_i, A_i, \{m_i(t) : t < T_i\}, T_i\}$$

and the observed data of patient i is

$$\mathcal{O}_i = \left\{X_i, A_i, \{Y_i(t_{ij}) : j = 0, \ldots, n_i\}, T_i\right\}.$$

Utility-based endpoint variable

For patient i, we define a utility function as follows:

$$u_i(t) = \begin{cases} m_i(t) & t < \min(T_i, L_i) \\ h_i(t) & T_i \leq t \leq L_i, T_i \leq L_i \\ 0 & t > L_i, T_i \leq L_i \end{cases}$$

where $h_i(t)$ is the post-event utility function.

Then, for patient i, the utility-based endpoint is defined as

$$U_i = \int u_i(t)dt.$$

Post-event utility function $h_i(t)$ i

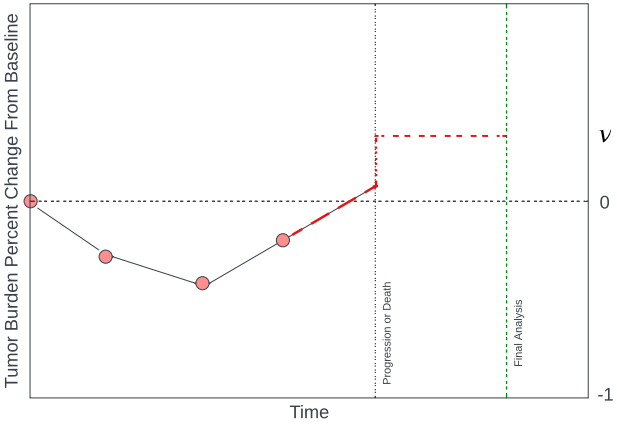
- The specification $m_i(t)$ can be data-driven
- The specification of $h_i(t)$, however, has to be based on the clinical question of interest

Post-event utility function $h_i(t)$ ii

- Consider progression or death as an intercurrent event (for tumor burden measurements) that is informative about the patient's outcome
- Then, the *composite variable strategy* can be applied to incorporate progression or death by

$$h_i(t) = \nu$$

Post-event utility function $h_i(t)$ iii



Further illustration of $h_i(t)$ i

- Set $m_i(t) \equiv 0$
- Then,

$$U_i = \int u_i(t)dt = \nu(L_i - T_i)I(T_i \leq L_i)$$

- Note

$$P(U_i \leq w|L_i;\Gamma) = P(T_i \geq L_i - \frac{w}{\nu}|L_i)$$

Further illustration of $h_i(t)$ ii

- Thus,

$$E(U_i|L_i) = \int_0^\infty (1 - P(U_i \leq w))dw = \int_0^\infty F_T(L_i - \frac{w}{\nu})dw$$
$$= \int_0^{\nu L_i} F_T(L_i - \frac{w}{\nu})dw$$
$$= \nu \int_0^{L_i} F_T(v)dv$$

and $\theta_a = E(U_i|A = a) = EE(U_i|L_i, A = a)$.

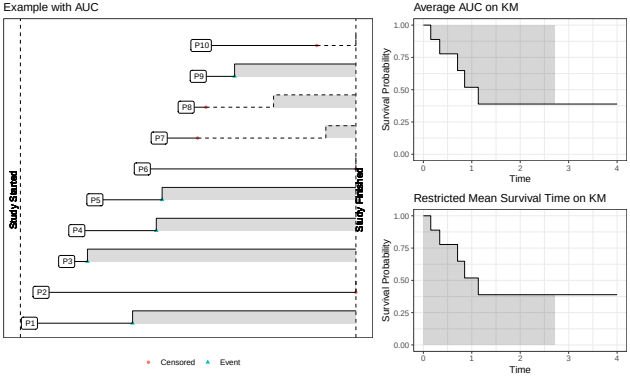
Further illustration of $h_i(t)$ iii

- Suppose we can approximate θ_a by

$$\theta_a = EE(U_i|L_i, A = a) \approx E(U_i|E(L_i|A = a), A = a)$$

- Then, for $\nu = 1$, θ_a can be interpreted as the compliment of the restricted mean survival time (RMST) until $E(L_i|A = a)$

Further illustration of $h_i(t)$ iv



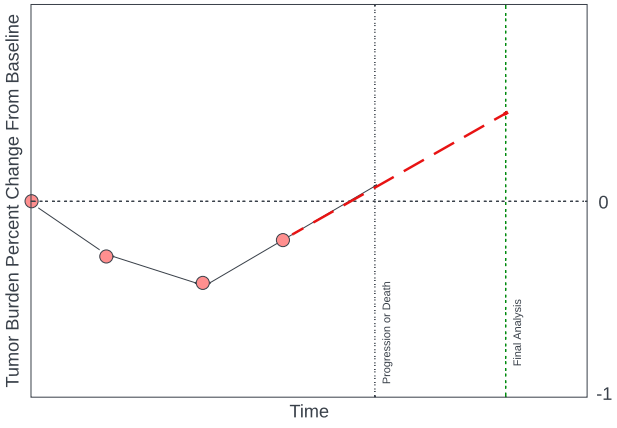
An estimand based on the composite variable strategy

- Thus, by setting $h_i(t) = \nu$, the total effect treatment effect becomes

$$\text{the effect on tumor burden} + \nu \times (1 - \text{RMST})$$

A hypothetical post-event utility function $h(t)$

- Setting $h(t) = m(t)$ applies the *hypothetical strategy* and assumes that that tumor burden curve hypothetically continues after progression or death



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Inference

- Estimate $\theta_a = E(U_i|A = a)$ by

$$\hat{\theta}_a = \frac{1}{\sum_{i=1}^{n} I(A_i = a)} \sum_{i=1}^{n} I(A_i = a) U_i \tag{1}$$

- Estimate the treatment effect $\theta = \theta_1 - \theta_0$ by by $\hat{\theta} = \hat{\theta}_1 - \hat{\theta}_0$
- Variance in $\hat{\theta}$ can be numerically evaluated (e.g., by bootstrap)
- The null hypothesis that the treatment does not have an effect can be tested by a Wald-type test

Probability models

Joint model factorization

- Let $f(S_i, Y_i | A_i, X_i)$ be the full model
- We factorize the full model as

$$f(S_i, Y_i | A_i, X_i) = f(S_i | A_i, X_i) f(Y_i | S_i, A_i, X_i)$$

- We model $f(S_i | A_i, X_i)$ and $f(Y_i | S_i, A_i, X_i)$ separately

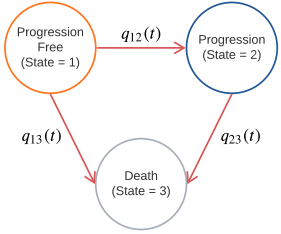
Missing data mechanism

- Let $R_{ij}(t)$ be the missing data indicator for $Y_{ij}(t)$
- We make the assumption that

$$f(Y_{mis}|R, Y_{obs}, S) = f(Y_{mis}|Y_{obs}, S)$$

Survival model

- Consider a parametric survival model (e.g., Weibull)
- Can be extended to a multi-state model



Tumor burden model (conditioning on survival)

- Let

$$\psi_{ij} = \frac{t_{ij}}{T_i}$$

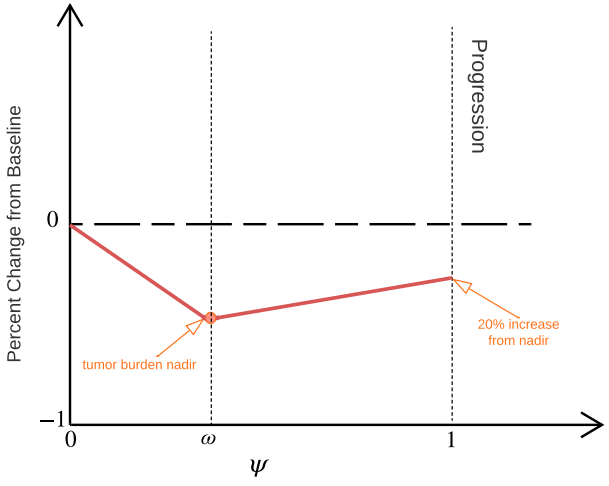
- Then, we model

$$Y_{ij}|X_i, T_i = m_i(\psi_{ij}) + \epsilon_{ij}$$

as a linear mixed model

  - where $\mathrm{E}\,\epsilon_{ij} = 0$, $\mathrm{Var}\,\epsilon_{ij} = \sigma^2$ and $\mathrm{Cov}(\epsilon_{ij}, \epsilon_{ij'}) = 0$ if $j \neq j'$

A pseudo tumor burden at progression and death



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To model $m_i(\psi_{ij})$, we specify:

$$
\begin{aligned}
m_i(\psi_{ij}) &= \gamma_1 \mathbf{X}_i + \gamma_2 A_i + b_{0,i} + b_{1,i}\psi_{ij} + b_{2,i}\psi_{ij}^2 \\
&= \begin{bmatrix} \gamma_1 \\ \gamma_2 \end{bmatrix} \begin{bmatrix} \mathbf{X}_i & A_i \end{bmatrix} + \begin{bmatrix} b_{0,i} \\ b_{1,i} \\ b_{2,i} \end{bmatrix} \begin{bmatrix} 1 & \psi_{ij} & \psi_{ij}^2 \end{bmatrix}
\end{aligned} \tag{2}
$$

A quadratic model approach ii

$b_{0,i}, b_{1,i}$ and $b_{2,i}$ are assumed to jointly follow Multivariate normal distribution, i.e.,

$$\begin{pmatrix} b_{0,i} \\ b_{1,i} \\ b_{2,i} \end{pmatrix} \sim MVN \left(\begin{pmatrix} b_0 \\ b_1 \\ b_2 \end{pmatrix}, \Sigma = \begin{pmatrix} \sigma_{00} & \sigma_{10} & \sigma_{20} \\ \sigma_{01} & \sigma_{11} & \sigma_{21} \\ \sigma_{02} & \sigma_{12} & \sigma_{22} \end{pmatrix} \right),$$

with the hyperparameters $b_0, b_1,$ and Σ given appropriate prior distributions.

Likelihood

$$L(\xi; \mathbf{Y}, \mathbf{X}, \mathbf{A}, \mathbf{S}) = \prod_{i=1}^{N} L(\gamma_1, \gamma_2, \mathbf{b}, \sigma^2, \Sigma; Y_{ij}, \mathbf{X}_i, A_i, S_i) L(\beta_{k_1,k_2}, \beta_A, \beta_X; S_i, \mathbf{X}_i, A_i)$$

An algorithm with data augmentation i

- Define $\xi^{(q)} = (\beta_{k_1,k_2}^{(q)}, \beta_A^{(q)}, \beta_X^{(q)}, \gamma_1^{(q)}, \gamma_2^{(q)}, \mathbf{b}_i^{(q)}, \mathbf{b}^{(q)}, \sigma^{2,(q)}, \Sigma^{(q)})$, $q \in \{1, ..., Q\}$, as the q^{th} posterior draw of the parameters, and set $\xi^{(0)}$ the initial value of the parameters

An algorithm with data augmentation ii

- **for** $q \in \{1, ..., Q\}$ **do:**
  1. Augment censored survival time from

$$S_{i,miss}^{(q+1)} \sim \propto p(S_{i,miss}|S_i, C_i, A_i, \mathbf{X}_i; \beta_{k_1,k_2}^{(q)}, \beta_A^{(q)}, \beta_X^{(q)}) \times p(Y_i|S_{i,miss}, S_i, A_i, \mathbf{X}_i; \gamma_1^{(q)}, \gamma_2^{(q)}, \mathbf{b}_i^{(q)}, \mathbf{b}^{(q)}, \sigma^{2,(q)}, \Sigma^{(q)})$$

  2. Draw parameters from the posterior

$$\xi^{(q+1)} \propto p(\beta_{k_1,k_2}, \beta_A, \beta_X|S_i, C_i, S_{i,miss}^{(q+1)}, A_i, \mathbf{X}_i) \times p(\gamma_1, \gamma_2, \mathbf{b}_i, \mathbf{b}, \sigma^2, \Sigma|S_i, S_{i,miss}^{(q+1)}, \mathbf{Y}_i, A_i, \mathbf{X}_i)$$

end for

An algorithm with data augmentation iii

- For each individual i, compute Q posterior samples of $U_i^q|\mathcal{O}_i, \mathbf{b}_i^q$, $q \in \{1, ..., Q\}$
- Estimate $U_i|\mathcal{O}_i \approx \frac{1}{Q}\sum_q U_i^q|\mathcal{O}_i, \mathbf{b}_i^q$
- Compute $\hat{\theta}_a = \frac{1}{n_a}\sum_{i=1}^{n_a} I_{\{A_i=a\}} U_i|\mathcal{O}_i$
- Tet C^* bootstrap posterior samples $\hat{\theta}_a^c, c \in \{1, ..., C^*\}$
- Compute C^* posterior samples for the treatment effect using $\hat{\theta}^c = \hat{\theta}_1^c - \hat{\theta}_0^c$

Illustrative Example

A hypothetical study

- Consider a randomized Phase III study for evaluating a PD-L1 monotherapy in non-small cell lung cancer patients
- There is a significant difference between treatment and control with respect to objective response, PFS and OS

A simulation study for power evaluation i

- Samples are drawn from the hypothetical study
- Conduct hypothesis testing based objective response, PFS, OS, and the proposed composite endpoint
- Power results are reported in the next table

A simulation study for power evaluation ii

Sample Size	ORR	PFS	OS	Composite	Hypothetical
100	0.48	0.62	0.27	0.87	0.58
200	0.88	0.96	0.61	0.99	0.95
300	0.99	0.99	0.90	1.00	1.00

Discussion

Discussion

- Novel estimands have been developed to leverage longitudinal tumor burden outcome in treatment effect evaluation for oncology trials
  - The estimand that takes the composite variable strategy for handling progression and death focuses on the total treatment effect on both tumor burden and survival
  - The estimand that takes the hypothetical strategy focuses on the biological mechanism of tumor growth
- The proposed methods do not aim to provide alternative "gold standard" of survival benefit in phase III confirmatory studies
  - The goal is to more efficiently quantify the signal of treatment effectiveness in an early phase cancer study, and to provide a novel framework for making go/no go decisions in oncology treatment development

Estimands in Observational Studies: Some Considerations beyond ICH E9 (R1)

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FDA/CDRH

Disclosures

No relevant disclosures

Overview

- Randomized controlled trials (RCT)
- Two basic assumptions for observational studies
- Causal estimands in observational studies
- Balancing weights
- Estimands often seen in the literature
- Choice of estimand

Notation

- Z -- the treatment assignment indicator
  - $Z = 1$ -- treated group
  - $Z = 0$ -- control group
- $(Y(1), Y(0))$ -- potential outcomes of a patient (treated and control)
- $X = (X_1, \dots, X_k)$ -- vector of covariates
- $e(x) = Pr(Z = 1|X = x)$ -- propensity score
- $f_1(x) = Pr(X = x|Z = 1)$ – conditional density of X in treated group
- $f_0(x) = Pr(X = x|Z = 0)$ – conditional density of X in control group
- $f(x) = Pr(X = x)$ – marginal density of X

Causal Estimands

Patient-level causal effect

$$Y(1)\ vs.\ Y(0)$$ (not simultaneously observable)

Population-level causal estimands

$distribution\ of\ Y(1)\ vs.\ distribution\ of\ Y(0)$ *on the same population*

Observed outcome

$$Y = Z\,Y(1) + (1 - Z)Y(0)$$

Randomized Controlled Trials (RCT)

Randomization

$(Y(1), Y(0)) \perp Z;\ Z = 1$ and $Z = 0$ represent the same population

Causal estimand in an RCT

$$Y(1)|Z = 1\ vs.\ Y(0)|Z = 1 \qquad or \qquad Y(1)|Z = 0\ vs.\ Y(0)|Z = 0$$

By randomization

$$Y(1)|Z = 1 \sim Y(1)|Z = 0 \qquad and \qquad Y(0)|Z = 1 \sim Y(0)|Z = 0$$

Hence the following defines a causal estimand (treatment effect)

$$Y(1)|Z = 1\ vs.\ Y(0)|Z = 0 \quad or \quad Y|Z = 1\ vs.\ Y|Z = 0$$

e.g. $$E(Y|Z = 1)\ vs.\ E(Y|Z = 0)$$

Estimator $$\bar{Y}_1\ vs. \bar{Y}_0$$

Basic Assumptions for Observational Studies

Unconfoundedness

$$(Y(1), Y(0)) \perp Z \mid X$$

(Conditional on X, the treatment assignment is essentially random)

Probabilistic treatment assignment

$$0 < e(x) = Pr(Z = 1|X = x) < 1$$

Causal Estimands

Local (or conditional) causal estimand

$$Y|Z = 1, X = x \quad vs. \quad Y|Z = 0, X = x$$

e.g., conditional treatment effect (causal estimand)

$$E(Y \mid Z = 1, X = x) \quad vs. \quad E(Y \mid Z = 0, X = x)$$

Weighted treatment effect (causal estimand)

$$\int E(Y|Z = 1, X = x)g(x)dx \quad vs. \quad \int E(Y|Z = 0, X = x)g(x)dx,$$

where $g(x)$ is a "weighting density function" (could be any probability density function)

ATE, ATT, ATC, etc.

$$\int E(Y|Z=1,X=x)g(x)dx \quad vs. \int E(Y|Z=0,X=x)g(x)dx,$$

- If $g(x) = f(x) = Pr(X=x)$ --- ATE.

  Population represented by all the patients in the study

- If $g(x) = f_1(x) = Pr(X=x|Z=1)$ --- ATT.

  Population represented by all the patients in the treated group

- If $g(x) = f_0(x) = Pr(X=x|Z=0)$ --- ATC

  Population represented by the patients in the control group

The Un-Weighted Estimator

Un-weighted estimators: $\bar{Y}_1 \; vs. \; \bar{Y}_0$ or $\frac{\sum_i Z_i Y_i}{\sum_i Z_i} \; vs. \frac{\sum_i (1-Z_i) Y_i}{\sum_i (1-Z_i)}$

Estimands of $\bar{Y}_1 and \; \bar{Y}_0$:

$$\bar{Y}_1 \; \rightarrow \int E(Y|Z=1, X=x) f_1(x) dx; \bar{Y}_0 \rightarrow \int E(Y|Z=0, X=x) f_0(x) dx,$$

where $f_1(x) = Pr(X=x|Z=1)$ and $f_0(x) = Pr(X=x|Z=0)$

Causal estimand:

$$\int E(Y|Z=1, X=x) g(x) dx \quad vs. \quad \int E(Y|Z=0, X=x) g(x) dx,$$

Weighted "Estimator"

Weighted "estimator:" $\bar{Y}_{1,w1} vs. \bar{Y}_{0,w0} = \frac{\sum_i w_1(X_i) Z_i Y_i}{\sum_i w_1(X_i) Z_i}$ $vs. \frac{\sum_i w_0(X_i)(1-Z_i) Y_i}{\sum_i w_0(X_i)(1-Z_i)}$

Estimand:

$$\int E(Y|Z=1, X=x) w_1(x) f_1(x) dx \; vs. \int E(Y|Z=0, X=x) w_0(x) f_0(x) dx,$$

If $w_1(x)$ and $w_0(x)$ satisfy

$$w_1(x) f_1(x) = w_0(x) f_0(x) = g(x),$$

then a comparison of the above two integrals defines a causal estimand, and these weights are called *balancing weights.*

Balancing Weights and Propensity Score

Defining equation for balancing weights:

$$w_1(x)f_1(x) = w_0(x)f_0(x) = g(x)$$

Bayes' theorem:

$$\frac{\Pr(X = x|Z = 1)}{\Pr(X = x|Z = 0)} = \frac{f_1(x)}{f_0(x)} \propto \frac{e(x)}{1-e(x)} = \frac{\Pr(Z = 1|X = x)}{\Pr(Z = 0|X = x)}$$

Hence

$$\frac{w_1(x)}{w_0(x)} \propto \frac{1 - e(x)}{e(x)}$$

A large class of balancing weights are functions of propensity score, and we call this class of balancing weights "principal balancing weights."

Balancing Weights for ATE

IPTW-ATE weights:

$$w_1^{(ATE)}(x) = \frac{1}{e(x)} \text{ and } w_0^{(ATE)}(x) = \frac{1}{1-e(x)}$$

By Bayes' theorem:

$$f_1(x)w_1^{(ATE)}(x) \propto f_0(x)w_0^{(ATE)}(x) \propto f(x) = g(x)$$

IPTW-ATE weights lead to the ATE population

Balancing Weights for ATT

IPTW-ATT weights:

$$w_1^{(ATT)}(x) = 1 \text{ and } w_0^{(ATT)}(x) = \frac{e(x)}{1-e(x)}$$

By Bayes' theorem:

$$f_1(x)w_1^{(ATT)}(x) \propto f_0(x)w_0^{(ATT)}(x) \propto f_1(x) = g(x)$$

IPTW-ATT weights lead to the ATT population

Balancing Weights for ATO

Overlap weights:

$$w_1^{(ATO)}(x) = 1 - e(x) \text{ and } w_0^{(ATO)}(x) = e(x)$$

By Bayes' theorem:

$$f_1(x)w_1^{(ATO)}(x) \propto f_0(x)w_0^{(ATO)}(x) \propto f(x)e(x)\big(1 - e(x)\big) = g(x)$$

The population corresponding to overlap weights is called ATO.

What's special about ATO?

Balance Diagnostics

Absolute standardized mean difference (ASMD)

$$d = \frac{|\bar{x}_{1,w1} - \bar{x}_{0,w0}|}{\sqrt{\frac{s^2_{1,w1} + s^2_{0,w0}}{2}}}$$

If d is large, then balancing weights are not that well-estimated

Balance criterion:

$$d \leq prespecified\ threshold$$

Overlap Weights Achieves Exact Balance

Theorem: When the propensity scores are estimated by maximum likelihood under a logistic regression model, the overlap weights lead to exact balance in the means of all included covariates between the treated and the control groups. (Li, Morgan and Zaslavsky, 2018)

Exact balance:

Absolute standardized mean difference (d) = 0

Attributes of estimand

- Treatment
- Population
  - for observational studies we need to choose between ATE, ATT, ATO, etc.
- Variable (or endpoint)
- Intercurrent event
- Population-level summary

Non-randomized study with external control

For example:

Treated group prospectively enrolled in traditional setting

Control group from a patient registry

The choice is often ATT

Concluding Remarks

The estimand should be prespecified for an observational study

Balancing weights correspond to population attribute of an estimand

Observational study with an external control group: often ATT

ATO more appropriate as supplementary analysis

References

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Thank You

Missing Data Introduced by Applying Hypothetical Strategies: Are They Really Missing?

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Outline

Overview

Goal:

- How to use the data after Intercurrent Event (ICE)

Review:

- ICH E9(R1) Guidelines
- Missing Data Imputation
- Causal Inference

Outcome:

- Propose a sensible approach to use the data after ICE

Motivation

Intercurrent Events (ICE)

- In most studies, a variety of post-randomization events can occur that mark a change in the course of treatment, for example,
  - Initiation of rescue therapy
  - Premature discontinuation of the randomized treatment, can be anticipated.
- Such events may influence the estimation and interpretation of treatment effects.
- These events are referred to as intercurrent events (ICEs) in ICH E9(R1)
  - The guideline stipulates that handling of these events needs to be described as part of the estimand definition.

Motivation

ICH E9(R1) suggested 5 strategies to handle ICEs:

- Treatment policy
- Composite
- While-on-treatment
- Hypothetical
- Principal stratification

Motivation

Hypothetical Strategy

- The purpose of most RCTs is to assess the efficacy and safety of an experimental treatment under the ideal situation (*i.e.*, without noncompliance, without dropout, and without rescue medication).
- However, it is often not possible to achieve the ideal situation due to ICEs. What is the average efficacy in the ideal situation when all patients would take the study medication as randomized? This corresponds to the estimand using a hypothetical strategy to handle ICEs, that is, using the potential outcome assuming patients would complete the assigned treatment without ICEs.

Motivation

Notation

- i: patient index $(= 1, \cdots, N)$
- t: time index $(= 0, \cdots, T)$
- Z_i: treatment
- X_i: covariates at the baseline
- M_{it}: Missing indicator ($M_{it} = 1$ if missing)
- Q_{it}: ICE indicator ($Q_{it} = 1$ if Intercurrent event (ICE))
  - $Q_{it} \equiv 0$: ICE does not happen at baseline ($t = 0$).
  - monotone: once ICE occurs at time t_*, then
    - $Q_{it} = 0$ for all $0 \leqslant t < t_*$ & $Q_{it} = 1$ for all $t_* \leqslant t < T$.
- Y_{it}; Observed outcome at time t

Motivation

Notation

- $Y_{it(q)}$; Potential outcome at time t under ICE q
  - At the baseline, we observe no ICE; we only observe $Y_{i0(0)}$ for all i
- $Y_{it} = Q_{it} Y_{it(0)} + (1 - Q_{it}) Y_{it(1)}$
- $\overleftarrow{Q}_{it} = (Q_{it}, Q_{it}, \cdots, Q_{it}) = \{Q_{is}\}_{s=0}^{t}$
- $\overrightarrow{Q}_{it} = (Q_{i,t+1}, Q_{i,t+2}, \cdots, Q_{iT}) = \{Q_{is}\}_{s=t+1}^{T}$
- $\overleftarrow{Y}_{it} = (Y_{i,t-1}, Y_{i1}, \cdots, Y_{it}) = \{Y_{is}\}_{s=0}^{t}$
- $\overrightarrow{Y}_{it} = (Y_{i,t+1}, Y_{i,t+2}, \cdots, Y_{iT}) = \{Y_{is}\}_{s=t+1}^{T}$
- $\mathcal{H}_{it} = \left\{\overleftarrow{Q}_{it}, \overleftarrow{Y}_{it}, \boldsymbol{X}_i\right\}$ $(e.g.\ \mathcal{H}_{i0} = \{Q_{i0}, Y_{i0}, \boldsymbol{X}_i\})$

Causal Graph

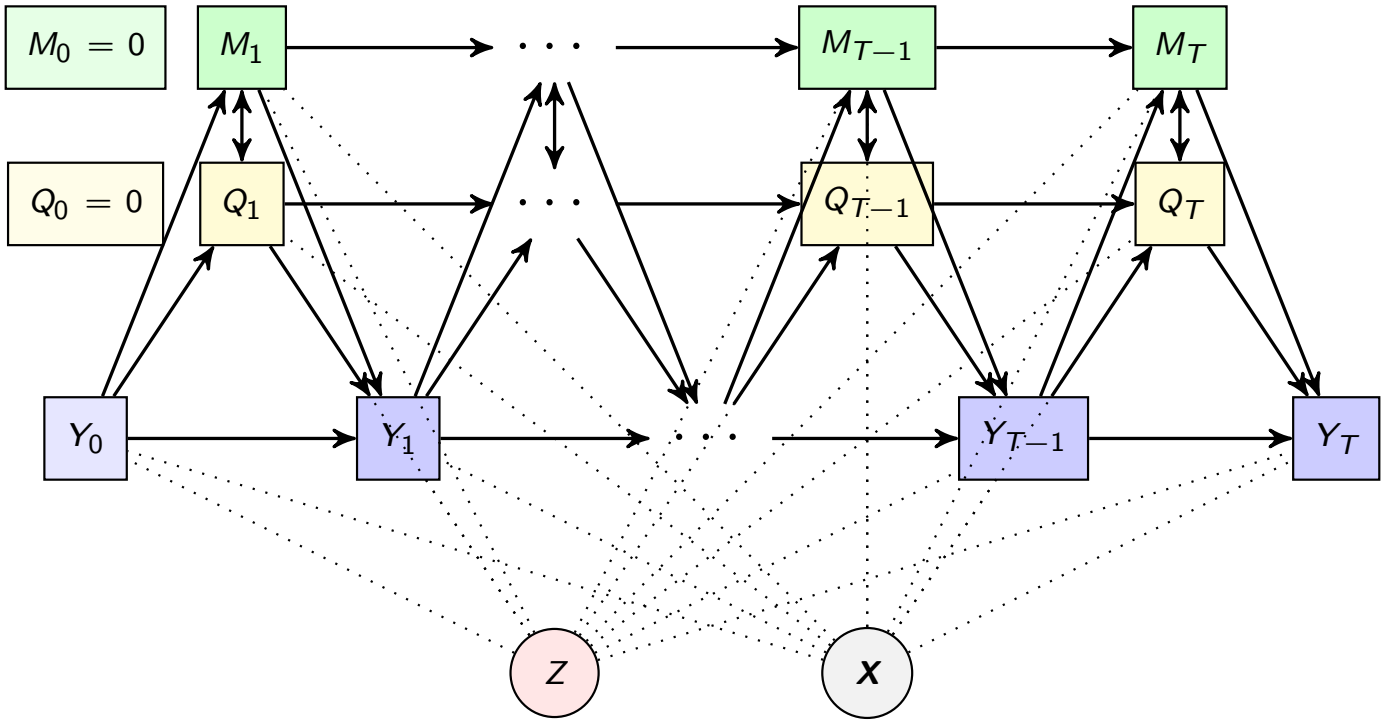

Figure: General Causal Graph

Motivation

Start with a simple setting:

- Monotone ICE only:
  - if ICE occurs for an individual i at time $t_*(>0)$, then $Q_{it} = 0$ for all $0 < t_* < t$ and $Q_{it} = 1$ for all $t_* \leqslant t \leqslant T$
- No missing data:
  - $M_{it} = 0$ for all t and i.
- single-arm study.
- No covariates.

Motivation

	Time				
id	t_0	t_1	t_2	t_3	$\cdots$
1					
2					
3					
4					
5					
6					
7					
8					
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$

- 'Blue' represents data before ICE;
- 'Orange' represents data after ICE;

Causal Graph for one measure post baseline

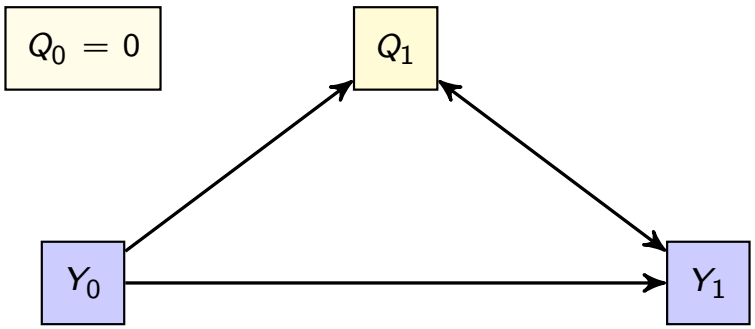

Figure: Causal Graph (2 time points with single arm & no missing)

Motivation (2 time points, single-arm, no covariates)

Table: 2 time points with single arm & no missing where $(\cdot)$: unobserved

	$t=0$			$t=1$		
i	$Q_{it} \equiv 0$	$Y_{it}(0)$	$Y_{it}(1)$	Q_{it}	$Y_{it}(0)$	$Y_{it}(1)$
1	0	5	$(\cdot)$	1	(κ)	15
2	0	5	$(\cdot)$	0	10	(15)
3	0	5	$(\cdot)$	0	200	(1000)

Goal: get a reasonable estimate for $Y_{11}(0) = \kappa$

- If we additionally have data $\{Y_{21}(1) = 15, Y_{31}(1) = 1000\}$, it is reasonable to assume κ close to 10 instead of random sample from $\{10, 200\}$.

Causal Graph for two measures post baseline

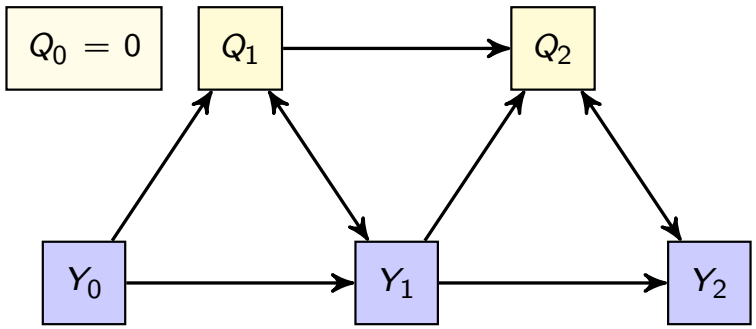

Figure: Causal Graph (3 time points with single arm & no missing)

Motivation (3 time points, single-arm, no covariates)

Table: 3 time points with single arm & no missing where $(\cdot)$: unobserved

	$t=0$			$t=1$			$t=2$		
i	$Q_{it} \equiv 0$	$Y_{it}(0)$	$Y_{it}(1)$	Q_{it}	$Y_{it}(0)$	$Y_{it}(1)$	Q_{it}	$Y_{it}(0)$	$Y_{it}(1)$
1	0	5	$(\cdot)$	1	(κ_1)	15	1	(κ_2)	25
2	0	5	$(\cdot)$	0	10	(15)	1	(κ_3)	25
3	0	5	$(\cdot)$	0	200	(1000)	0	300	(1200)

Goal: obtain values from

- $Y_{11}(0) = \kappa_1$ from $\{Y_{11}(0) | Y_{11}(1), Q_{11} = 1, Y_{10}\}$
- $Y_{12}(0) = \kappa_2$ from $\{Y_{12}(0) | Y_{12}(1), Q_{12} = 1, Q_{11} = 1, Y_{11}, Y_{10}\}$
- $Y_{22}(0) = \kappa_3$ from $\{Y_{22}(0) | Y_{22}(1), Q_{22} = 1, Q_{21} = 0, Y_{21}, Y_{20}\}$

* but **NOT** identified

- **MCAR**

$$\mathrm{P}\left(M_{it}=1|\overleftarrow{Y}_{i,t-1},\overrightarrow{Y}_{it}\right)=\mathrm{P}(M_{it}=1)$$

- **MAR**

$$\mathrm{P}\left(M_{it}=1|\overleftarrow{Y}_{i,t-1},\overrightarrow{Y}_{it}\right)=\mathrm{P}\left(M_{it}=1|\overleftarrow{Y}_{i,t-1}\right)$$

- **MNAR**

$$\mathrm{P}\left(M_{it}=1|\overleftarrow{Y}_{i,t-1},\overrightarrow{Y}_{it}\right)=\mathrm{P}\left(M_{it}=1|\overleftarrow{Y}_{i,t-1},\overrightarrow{Y}_{it}\right)$$

1. **Stable Unit Treatment Value Assumption (SUTVA)**
   - If $Z_i = z'$, then $Y_i(\boldsymbol{Z}) = Y_i(z')$
   - SUTVA implies that potential outcomes for each person i are unrelated to the treatment status of other individuals. This assumption allows us to write $Y_i(\boldsymbol{Z})$ as $Y_i(Z_i)$.
2. **Consistency**
   - For $z \in \{0, 1\}$,

$$\{Y_i(z) | Z_i = z, \boldsymbol{X}_i\} = \{Y_i | Z_i = z, \boldsymbol{X}_i\}$$

3. **Ignorability**

$$\{Y_i(0), Y_i(1)\} \perp\!\!\!\perp Z_i | \boldsymbol{X}_i$$

4. **Positivity**

$$0 < \mathrm{P}(Z_i = 1 | \boldsymbol{X}) < 1$$

5. **Gaussian copula model**

$$\begin{aligned}&\mathrm{F}\left(Y_{it}(1), Y_{it}(0) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\\&= \Phi_2\left\{\Phi_1^{-1}\left\{\mathrm{F}\left(Y_{it}(1) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\right\}, \Phi_1^{-1}\left\{\mathrm{F}\left(Y_{it}(0) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\right\}; \rho\right\}.\end{aligned}$$

where $\mathrm{F}(\cdot)$ is the joint distribution function, Φ_1 is the univariate CDF, and Φ_2 is the bivariate CDF with mean 0 and correlation parameter ρ between outcomes (ρ: sensitivity parameter)

- Note that this construction of the joint distribution of the outcomes puts no restrictions on the models for the marginals.

$\Rightarrow$ *Adopt all this to ICEs*

Assumptions for ICE

- **ICAR (Intercurrent Completely at Random)**

$$\mathrm{P}(Q_{it} = 1 | Y_{it}(1), Y_{it}(0), \mathcal{H}_{i,t-1}) = \mathrm{P}(Q_{it} = 1)$$

- **IAR (Intercurrent at Random)**

$$\mathrm{P}(Q_{it} = 1 | Y_{it}(1), Y_{it}(0), \mathcal{H}_{i,t-1}) = \mathrm{P}(Q_{it} = 1 | \mathcal{H}_{i,t-1})$$

- **INAR (Intercurrent Not at Random)**

$$\mathrm{P}(Q_{it} = 1 | Y_{it}(1), Y_{it}(0), \mathcal{H}_{i,t-1})$$

From a causal perspective, the idea that ICE at time t depends only on history up to time t seems reasonable in many settings. (IAR)

Assumptions for ICE

1. **Stable Unit Treatment Value Assumption (SUTVA)**
   - If $Z_i = z$, then $Q_i(\boldsymbol{Z}) = Q_i(z)$
   - If $Z_i = z$ and $Q_i = q$, then $Y_i(\boldsymbol{Z}, \boldsymbol{Q}) = Y_i(z, q)$
2. **Consistency**
   - For any $z \in \{0, 1\}$ and $q \in \{0, 1\}$,

$$\{Y_{it}(z, q) | Z_{it} = z, Q_{it} = q\} = \{Y_{it} | Z_i = z, Q_{it} = q\}$$

3. **Ignorability**

$$\{Y_{it}(0), Y_{it}(1)\} \perp\!\!\!\perp Q_{it} | \mathcal{H}_{i,t-1} \text{ where } \mathcal{H}_{i,t-1} = \left\{ \overleftarrow{Q}_{i,t-1}, \overleftarrow{Y}_{i,t-1}, \boldsymbol{X}_i \right\}$$

4. **Positivity**

$$0 < \mathrm{P}\left(Q_{it} = 1 | \overleftarrow{Q}_{i,t-1} = \mathbf{0}_{t \times 1}, \overleftarrow{Y}_{i,t-1}, \boldsymbol{X} \right) < 1$$

Assumptions for ICE

5. **Gaussian copula model**

$$\begin{aligned}&\mathrm{F}\left(Y_{it}(1), Y_{it}(0) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\\&= \Phi_2\left\{\Phi_1^{-1}\left\{\mathrm{F}\left(Y_{it}(1) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\right\}, \Phi_1^{-1}\left\{\mathrm{F}\left(Y_{it}(0) \,|\, Q_{it}=1, \mathcal{H}_{i,t-1}\right)\right\}; \rho\right\}.\end{aligned}$$

where $\mathrm{F}(\cdot)$ is the joint distribution function, Φ_1 is the univariate CDF, and Φ_2 is the bivariate CDF with mean 0 and correlation parameter ρ between outcomes (ρ: sensitivity parameter).

Model

Goal: Identify

$$\{Y_{it}(0) \,|\, Y_{it}(1), Q_{it} = 1, \mathcal{H}_{i,t-1}\}$$

- Under the consistency assumption (Assumption 2),

$$\{Y_{it}(0) \,|\, Q_{it} = 0, \mathcal{H}_{i,t-1}\} = \{Y_{it} | Q_{it} = 0, \mathcal{H}_{i,t-1}\},$$
$$\{Y_{it}(1) \,|\, Q_{it} = 1, \mathcal{H}_{i,t-1}\} = \{Y_{it} | Q_{it} = 1, \mathcal{H}_{i,t-1}\}.$$

- Under the ignorability assumption (Assumption 3),

$$\{Y_{it}(q) \,|\, Q_{it} = q, \mathcal{H}_{i,t-1}\} = \{Y_{it}(q) \,|\, Q_{it} = q', \mathcal{H}_{i,t-1}\} \quad \text{for } q, q' \in \{0, 1\}.$$

$\Rightarrow$ Two identified marginal distributions:

$$\{Y_{it}(0) \,|\, Q_{it} = 1, \mathcal{H}_{i,t-1}\} \quad \text{and} \quad \{Y_{it}(1) \,|\, Q_{it} = 1, \mathcal{H}_{i,t-1}\}$$

Model

- Joint by Gaussian Copula (Assumption 5),

$$\mathrm{P}(Y_{it}(0)\,|Q_{it}=0,\mathcal{H}_{i,t-1}) \overset{\mathrm{d}}{=} \mathrm{F}(Y_{it}(0)\,|Q_{it}=0,\mathcal{H}_{i,t-1};\theta_{it}(0))$$
$$\mathrm{P}(Y_{it}(1)\,|Q_{it}=1,\mathcal{H}_{i,t-1}) \overset{\mathrm{d}}{=} \mathrm{F}(Y_{it}(1)\,|Q_{it}=1,\mathcal{H}_{i,t-1};\theta_{it}(1))$$

Finally, we have

$$\begin{aligned}&\mathrm{F}(Y_{it}(1),Y_{it}(0)\,|Q_{it}=1,\mathcal{H}_{i,t-1})\\&=\Phi_2\left\{\Phi_1^{-1}\left\{\mathrm{F}(Y_{it}(1)\,|Q_{it}=1,\mathcal{H}_{i,t-1})\right\},\Phi_1^{-1}\left\{\mathrm{F}(Y_{it}(0)\,|Q_{it}=1,\mathcal{H}_{i,t-1})\right\};\rho\right\}.\end{aligned}$$

Model

e.g.

- Again, we can estimate from the observed data (under consistency):

$$\{Y_{it}|Q_{it}=0,\mathcal{H}_{i,t-1}\} \quad \text{and} \quad \{Y_{it}|Q_{it}=1,\mathcal{H}_{i,t-1}\}.$$

- Assume

$$\mathsf{P}(Y_{it}|Q_{it}=0,\mathcal{H}_{i,t-1}) \overset{\mathsf{d}}{=} \mathsf{N}\left(\mu_{it}(0)=\mathbb{X}_{it}\beta_{it}(0),\sigma_{it}(0)^2\right)$$
$$\mathsf{P}(Y_{it}|Q_{it}=1,\mathcal{H}_{i,t-1}) \overset{\mathsf{d}}{=} \mathsf{N}\left(\mu_{it}(1)=\mathbb{X}_{it}\beta_{it}(1),\sigma_{it}(1)^2\right)$$

- Under ignorability,

$$\begin{aligned}\mathsf{P}(Y_{it}(0)|Q_{it}=1,\mathcal{H}_{i,t-1}) &\overset{\mathsf{d}}{=} \mathsf{P}(Y_{it}(0)|Q_{it}=0,\mathcal{H}_{i,t-1}) \\ &\overset{\mathsf{d}}{=} \mathsf{N}\left(\mu_{it}(0)=\mathbb{X}_{it}\beta_{it}(0),\sigma_{it}(0)^2\right)\end{aligned}$$

Simulation

- **Observed outcome at time 0 (no ICE);** $Y_{i0}|\mathcal{H}_{i0}$

- $Y_{i0} \sim \mathrm{N}\left(\mu_0, \sigma_0^2\right)$

- **Potential Outcomes at time** t**;** $\left\{Y_{it}(0), Y_{it}(1) \,|\mathcal{H}_{i,t-1}\right\}$

- $\begin{pmatrix} Y_{it}(0) & Y_{it}(1) \end{pmatrix} \sim \mathrm{MVN}(\boldsymbol{\mu}_{it}, \boldsymbol{\Sigma}_{it})$ where

$$\boldsymbol{\mu}_{it(\cdot)} = \begin{pmatrix} \boldsymbol{\mu}_{it}(0) \\ \boldsymbol{\mu}_{it}(1) \end{pmatrix} \text{ and } \boldsymbol{\Sigma}_{it} = \begin{pmatrix} \boldsymbol{\sigma}_{it}(0)^2 & \rho\boldsymbol{\sigma}_{it}(0)\boldsymbol{\sigma}_{it}(1) \\ \rho\boldsymbol{\sigma}_{it}(0)\boldsymbol{\sigma}_{it}(1) & \boldsymbol{\sigma}_{it}(1)^2 \end{pmatrix}$$

where $\boldsymbol{\mu}_{it}(0)$, $\boldsymbol{\mu}_{it}(1)$, $\boldsymbol{\sigma}_{it}(0)$ and $\boldsymbol{\sigma}_{it}(1)$ are set from the models in the previous page. We set the correlation parameter $\rho = 0.3$.

- **ICE indicator at time** t

- $Q_{it}|\cdot \sim \mathrm{Bernoulli}(\pi_{it}(\cdot))$, *i.e.*, $\mathrm{P}(Q_{it} = 1|\cdot) = \pi_{it}(\cdot)$ where

$$\pi_{it}(\cdot) = \Phi\left(\alpha_t + \gamma_{t-1}\left(Y_{i,t-1} - \mu_{i,t-1}\right) + \omega_t\left(Y_{it}(0) - Y_{it}(1)\right)\right)$$

Simulation Setting

For $N = 1000$,

- $t = 0$
  - $\mu_0 = 100$, $\sigma_0^2 = 20$
- $t = 1$
  - $\boldsymbol{\mu}_{i1}(0) = \lambda_1(0) Y_{i0} = 0.97 Y_{i0}$ and $\boldsymbol{\sigma}_{i1}(0)^2 = 10$
  - $\boldsymbol{\mu}_{i1}(1) = \lambda_1(1) Y_{i0} = 0.99 Y_{i0}$, and $\boldsymbol{\sigma}_{i1}(1)^2 = 15$
  - $\rho_1 = 0.3$
  - $\alpha_1 = -5.85$, $\gamma_1 = 1$, $\omega_1 = 0$ (IAR)

  $\Rightarrow$ ICE rate: about 10%
- $t = 2$
  - $\boldsymbol{\mu}_{i2}(0) = \lambda_2(0) Y_{i1} = 0.97 Y_{i1}$ and $\boldsymbol{\sigma}_{i2}(0)^2 = 10$
  - $\boldsymbol{\mu}_{i2}(1) = \lambda_2(1) Y_{i1} = 0.99 Y_{i1}$, and $\boldsymbol{\sigma}_{i2}(1)^2 = 15$
  - $\rho_2 = 0.3$
  - $\alpha_2 = -6.6$, $\gamma_2 = 1$, $\omega_2 = 0$ (IAR)

  $\Rightarrow$ ICE rate: about 20%

Simulation Result

Compare: $\mathrm{E}\left[Y_{it}(0) \mid Q_{it}=1, \mathcal{H}_{i,t-1}\right]$ vs. $\mathrm{E}\left[Y_{it}(0) \mid Y_{it}(1), Q_{it}=1, \mathcal{H}_{i,t-1}\right]$;

t_1	N	BVN								
		ρ_1	ρ_2	ρ_3	ρ_4	ρ_5	ρ_6	ρ_7	ρ_8	ρ_9
Bias	0.0004	0.0004	0.0003	0.0010	0.0024	0.0013	0.0010	0.0006	0.0001	0.0005
Var	***0.2670***	0.2647	0.2624	0.2572	0.2514	0.2416	0.2313	0.2172	0.2033	0.1865
MSE	***0.2670***	0.2647	0.2624	0.2572	0.2514	0.2416	0.2313	0.2172	0.2033	0.1865
	ρ_0	ρ_{-1}	ρ_{-2}	ρ_{-3}	ρ_{-4}	ρ_{-5}	ρ_{-6}	ρ_{-7}	ρ_{-8}	ρ_{-9}
Bias	0.0005	0.0009	0.0007	0.0001	0.0015	0.0002	0.0012	0.0000	0.0009	0.0002
Var	0.2655	0.2659	0.2612	0.2588	0.2500	0.2417	0.2311	0.2181	0.2025	0.1865
MSE	0.2655	0.2659	0.2612	0.2588	0.2500	0.2417	0.2311	0.2181	0.2025	0.1865
t_2		ρ_1	ρ_2	ρ_3	ρ_4	ρ_5	ρ_6	ρ_7	ρ_8	ρ_9
Bias	0.0015	0.0013	0.0006	0.0004	0.0006	0.0010	0.0013	0.0009	0.0008	0.0018
Var	***0.2941***	**0.2945**	**0.2969**	0.2921	0.2879	0.2843	0.2767	0.2720	0.2629	0.2538
MSE	***0.2941***	**0.2945**	**0.2969**	0.2921	0.2879	0.2843	0.2767	0.2720	0.2629	0.2538
	ρ_0	ρ_{-1}	ρ_{-2}	ρ_{-3}	ρ_{-4}	ρ_{-5}	ρ_{-6}	ρ_{-7}	ρ_{-8}	ρ_{-9}
Bias	0.0026	0.0007	0.0009	0.0018	0.0009	0.0020	0.0002	0.0010	0.0005	0.0003
Var	**0.2952**	0.2929	0.2939	0.2916	0.2872	0.2816	0.2763	0.2692	0.2613	0.2522
MSE	**0.2952**	0.2929	0.2939	0.2916	0.2872	0.2816	0.2763	0.2692	0.2613	0.2522

- 100,000 data set were generated
- $\rho_k = \frac{k}{10}$, $k \in \{-9, -8, \cdots, 0, 1, \cdots, 9\}$ (sensitivity parameter ρ)
- used a single imputation method (for simplicity)

Future Work

- Real Data Application
- Priors for sensitivity parameter ρ
- Missing Data
- Semiparametric, Non-parametric, Bayesian Approach
- INAR (Intercurrent not at random) mechanism

References

- ICH E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials Guidance for Industry, *Food and Drug Administration (FDA)* (2021)
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- Initiation of Symptomatic Medication in Alzheimer's Clinical Trials: Hypothetical versus Treatment Policy Approach, *Donohue* (2020)
- Defining estimands using a mix of strategies to handle intercurrent events in clinical trials, *Qu* (2020)

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- I would like to thank my manager, Chenguang (CG) Wang, who gave me helpful advice and instructions.

- Thank you for listening!

Statistical considerations in constructing estimands for clinical trial design and analysis: addressing issues beyond intercurrent events

May 23, 2023

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SCT
SOCIETY FOR CLINICAL TRIALS

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O'NEAL COMPREHENSIVE CANCER CENTER

ESTIMANDS

- Randomized controlled trials are the gold standard for determining the efficacy of a new intervention. Trials conducted for regulatory approval of an intervention compare the effect of the intervention with the standard of care or placebo to demonstrate efficacy. Randomization attempts to ensure that all known and unknown confounding factors are evenly distributed between the groups, and that the groups will be comparable at the end of the study, so that any inter-group differences in outcomes can be attributed to the intervention. However, in reality, intercurrent events may impact the assessment and subsequent interpretation of the outcome of interest. To address this:
- In August 2017, ICH released an addendum to E9 (ICH E9 R1) which put forth the concept of “Estimands and Sensitivity Analysis in Clinical Trials.”
- November 2019 Final version of the appendum ICH E9 R1,
- Accepted and adopted by the US FDA.
- July 2020, Health Canada endorsed the principles and suggested adoption

VARIOUS ESTIMAND STRATEGIES

- **Treatment policy strategy** – value of the outcome of interest regardless of the occurrence of the intercurrent event- the intention to treat analysis
- **Composite strategy** – value of the variable with the intercurrent event being woven into the outcome variable
- **Hypothetical strategy** – assumes that the intercurrent event did not happen in patients who were randomized
- **Principal stratum strategy** – measurement of the variable of interest is a subgroup of patients not likely to need rescue medication or not likely to discontinue treatment
- **While on treatment strategy** – measurements up until the time of the event particularly when the measurements are repeated at multiple time points

DR. LI

ESTIMANDS IN OBSERVATIONAL STUDIES: SOME CONSIDERATIONS BEYOND ICH E9

- Randomized controlled trials (RCT)
- Two assumptions for observational studies
- Causal estimands in observational studies
- Balancing weights (all the patients in the study: ATE; ATT; ATC) & Propensity Score
- Balance Diagnostics; Absolute standardized mean difference (ASMD)
- Estimands often seen in the literature
- Choice of estimand: The estimand should be prespecified for an observational study

Balancing weights correspond to population attribute of an estimand

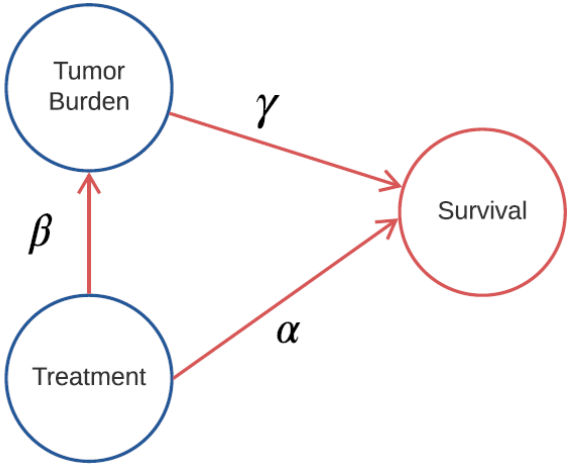
Observational study with an external control group: often ATT

ATO (The population corresponding to overlap weights) more appropriate as supplementary analysis

QUESTIONS:

- Since November 2019 Final version of the appendum ICH E9 R1, how many clinical trial protocols have bee submitted for approval with this approach?
- Did they spell out all the components? Some estimand framework requires the sponsor and investigators think though about the various possible intercurrent events and their combinations well in advance and address these a priori while planning the study and explicitly state these in the protocol in a separate section called the estimands?

DR. WANG
A TUMOR BURDEN–INTEGRATED ESTIMAND FOR CANCER CLINICAL STUDIES



- Evaluating treatment effect in early phase clinical studies based on tumor burden and survival, i.e., *the totality of the information*
- Do *not* set the goal to understand α, β and γ individually
- Instead, propose to evaluate the *total treatment effect* (approximately); $\mathcal{E} = \alpha + \beta\gamma$

- Simulation study consider progression or death as an intercurrent event (for tumor burden measurements) that is informative about the patient's outcome
- Then, the *composite variable strategy* in the FDA ICH E9 (R1) guidance was applied to incorporate progression or death by
- $h_i(t) = \nu$
- Simulation study:
- A multisate model incorporated piecewise linear mixed model
- Conduct hypothesis testing based objective response, PFS, OS, and the proposed composite endpoint
- Power results are reported

- Efficiency in hypothesis testing based on the endpoint variables of the new estimands has been demonstrated in preliminary analysis
- The proposed new estimands its goal is to more efficiently quantify the signal of treatment effectiveness in a cancer study,

QUESTIONS:

- Cost/Benefit for incorporating the estimands?

BAE

- **Missing Data Introduced by Applying Hypothetical Strategies: Are They Really Missing?**

Simulation study:
ICAR (Intercurrent Completely at Random)
IAR (Intercurrent at Random)
INAR (Intercurrent Not at Random)

Causal Graph

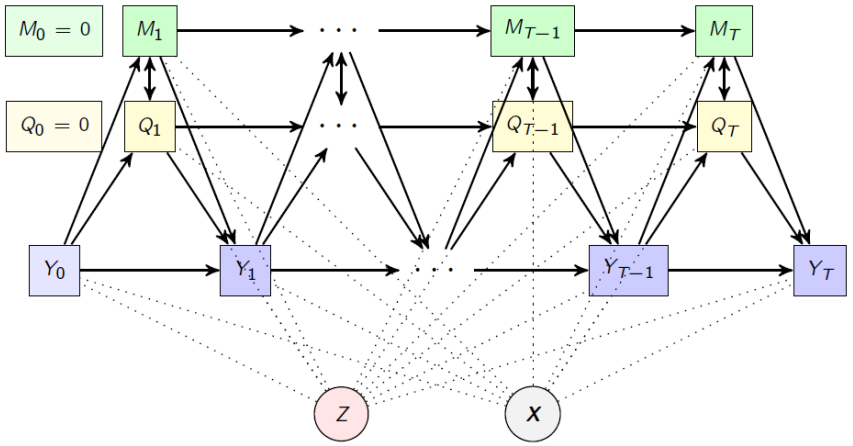


Figure: General Causal Graph

ESTIMANDS:

The importance of the ICH E9 R1 addendum lies in the clarity that it provides in assessing trial results, through the use of guidance and a framework for addressing intercurrent events. The choice of estimand(s) in a trial will be driven by the therapeutic area, characteristics of the intervention, alternative therapies available and the characteristics of the population being studied. The estimands framework helps think about various intercurrent events at the planning and design stage itself, so that these do not impact conclusions about whether or not an intervention actually works or is likely to work in the real-world setting (efficacy vs. effectiveness).

Q&A