

Using a mix of strategies in handling intercurrent events and missing values for studies impacted by the COVID-19 pandemic

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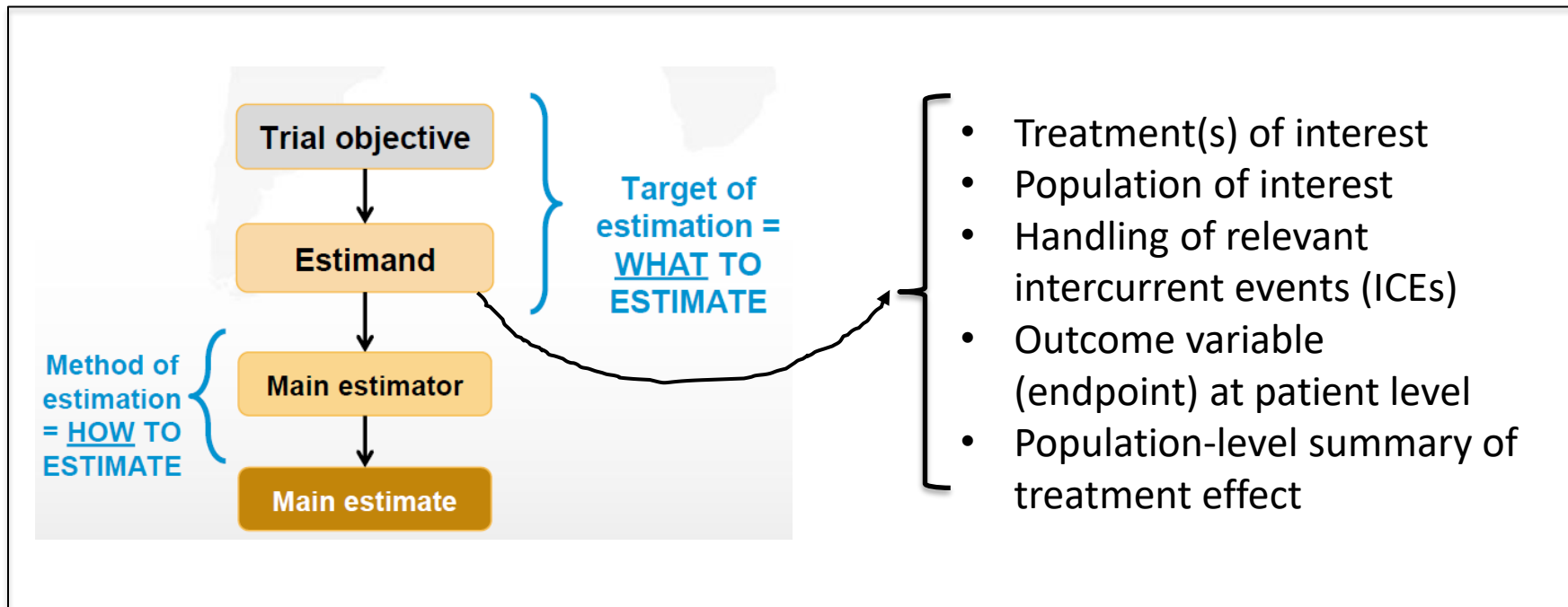
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This presentation is based on the joint work with Linda Shurzinske, Shanthi Sethuraman, Ilya Lipkovich, and Wei Shen



Estimand framework [ICH E9 (R1)]

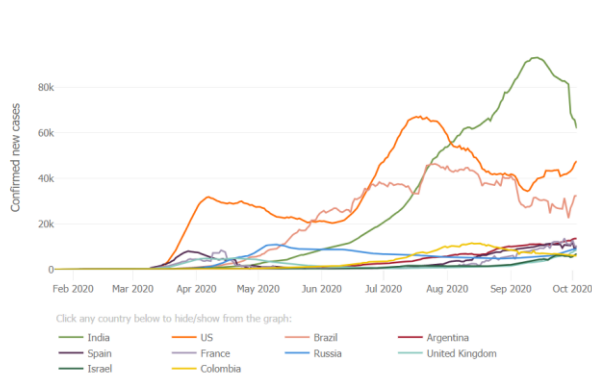


ICE, intercurrent events

Potential ICEs and missing values related to the COVID-19 pandemic

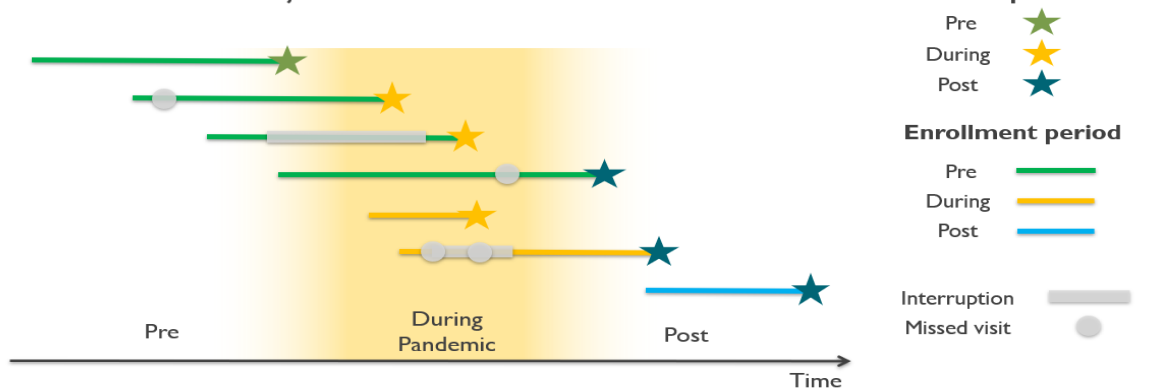
DAILY CONFIRMED NEW CASES (7-DAY MOVING AVERAGE)

Outbreak evolution for the current 10 most affected countries



<https://coronavirus.jhu.edu/data/new-cases>

Potential individual subject courses:



Fletcher, C. and Meyer, R.D. (2020), DIA presentation

- Prolonged treatment interruptions due to COVID-19 illness or controlled measures (e.g., quarantines, travel restrictions, etc).
- Study treatment discontinuations due to COVID-19 illness (an adverse events [AE]) or controlled measures.
- Death as a result of COVID-19 illness
- Use of protocol prohibited medications to treat COVID-19 illness
- In addition to the ICEs, COVID-19 may also cause missing values

Strategies to handle ICEs

- Treatment policy
- Hypothetical
- Composite variable
- While on treatment (WOT)
- ***Principal stratum (PS)***

- ICH E9 (R1) provides a framework for defining estimand
- Key components to be considered
 - Treatment(s) of interest
 - ***Population of interest***
 - Handling of relevant intercurrent events (ICEs)
 - Outcome variable (endpoint) at patient level
 - Population-level summary of treatment effect

- PS is to define a population, not a strategy to handle ICEs (although ICEs can be used to define PS)
- PS (defining a subset) can be combined with any other strategies to handle ICEs

ICE, intercurrent events

Defining estimands based on potential outcomes in causal-inference framework (Neyman, 1923; Pearl, 2009; Lipkovich, et al., 2020)

- Y : outcome of interest
- S : stratum (subset) of the population, and n is the sample size for S
- A : treatment (0 = control; 1 = experimental treatment)
- $Y(a, b)$: the PO of Y assigned to treatment a but actually taking b
 - As we will see, actual treatment is a PO on its own and can depend on intermediate outcomes of initial treatment, $Z(a)$
- The **causal** estimand for a subset S if patient would adhere to their assigned treatment is the average treatment effect (ATE)

$$\frac{1}{n} \sum_{i=1}^n E[Y_i(1,1) - Y_i(0,0)|S] \quad \longrightarrow \quad E[Y_i(1,1) - Y_i(0,0)|S]$$

Subscript i may be omitted to simplify the notation

- For the whole population (all randomized patients), we may remove S

$$E[Y_i(1,1) - Y_i(0,0)]$$

PO, potential outcome

Treatment policy strategy

- ICH E9 (R1) describes the treatment policy strategy as “the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.”
- Let $A_i^* = \{A_i, g_i(Z_i(A_i))\}$ be the treatment regimen (policy) patient i takes
 - g_i maps intermediate outcomes Z_i to a treatment regimen (i.e., stopping study meds when having AE)
 - g_i generally is not precisely defined in the protocol (certain things may be left to physician’s discretion)
- The estimand using this **treatment policy** strategy is defined by

$$E \left\{ Y_i \left(1, g_i(Z_i(1)) \right) - Y_i \left(0, g_i(Z_i(0)) \right) \right\} \longrightarrow g() \text{ with subscript } i$$

- Estimand for the **dynamic treatment regimen** (DTR) (Murphy et al., 2001; Moodie et al., 2007)

$$E \left\{ Y_i \left(1, g(Z_i(1)) \right) - Y_i \left(0, g(Z_i(0)) \right) \right\} \longrightarrow g() \text{ without subscript } i$$

The time-varying treatment regimen function g is defined clearly and in a same way for all patients

Strategies to Handle ICEs

	Reasons for Strategy to Be Avoided in Handling ICEs
While on Treatment	The scope of WOT is limited to cases when the focus is on patient's well-being measured in a period impacted not by the ICE, which is a rare situation.
Composite	Recommend explicitly including the relevant events as part of the endpoint definition (e.g., “treatment failure is defined as not meeting the goal of ACR20 at 12 weeks, or use of a rescue medication in the first 12 weeks)
Treatment Policy	<p>Blindly taking whatever outcomes regardless of the cause of ICEs is not a good strategy. If the outcome after ICEs is aligned with study objective, such ICEs should be included in the treatment regimen of interest.</p> <p>For example, the treatment of interest is the randomized treatment with additional rescue medication allowed in the protocol. Then, use of the protocol-defined rescue medication is not an ICE (i.e. not a deviation from treatment of interest).</p> <p>Many issues arose from the COVID-19 pandemic because the protocols specify the use of treatment policy for <i>all</i> ICEs [not defining $g(\cdot)$ explicitly]</p>
Principal Stratum	A strategy for defining subpopulation of interest, not a strategy to handle ICEs

As estimands should be defined in terms of the potential outcome, most strategies in handling ICEs should be “hypothetical”

Controlled direct hypothetical (CDH) strategy

- The PO of interest is the outcome if patients could complete the treatment event in the presence of ICEs

- The estimand is

$$E\{Y_i(1,1) - Y_i(0,0)\}$$

- “Controlled direct” was borrowed from *controlled direct effect* (Pearl, 2009)
- This approach may be appropriate for
 - ICEs due to administrative reasons (e.g., treatment discontinuation due to patient relocation, ICEs related to COVID-19 controlled measures)
 - ICEs that do not represent the “normal” time (e.g., COVID-19 illness)
 - ICEs due to LoE

LoE, lack of efficacy; PO, potential outcome

No treatment hypothetical (NTH) strategy

- The PO of interest is the outcome assuming patients with ICEs would have no benefit from the treatment (as if the patients were left untreated starting from randomization):

$$E[\{Y_i(1, -1)\Delta_i(1) + Y_i(1, 1)(1 - \Delta_i(1))\} - \{Y_i(0, -1)\Delta_i(0) + Y_i(0, 0)(1 - \Delta_i(0))\}]$$

where “-1” in the second parameter $Y_i(\cdot, \cdot)$ indicates no treatment received and $\Delta_i(a)$ is the ICE indicator (0 for no ICE and 1 for ICE occurring).

- This approach may be appropriate for ICEs due to AE (occurring at “normal time”)

AE, adverse event; ICE, intercurrent events; PO, potential outcome

Partial treatment hypothetical (PTH) strategy

- The PO of interest is the outcome if the patient can benefit from (or be harmed by) the study medication until the ICE and then stops taking the medication.
- The estimand is defined as

$$E\left[\left\{Y_i(1, g_i(T_i(1)))\Delta_i(1) + Y_i(1,1)(1 - \Delta_i(1))\right\} - \left\{Y_i(0, g_i(T_i(0)))\Delta_i(0) + Y_i(0,0)(1 - \Delta_i(0))\right\}\right]$$

where $T_i(a)$ is the time to the ICE under treatment a and $g_i(T_i(a))$ is the treatment regimen: taking treatment a until the occurrence of the ICE and then having no access to treatment until a specified assessment time.

- This strategy may be suitable for handling ICEs due to AE at a “normal circumstances” (not for AE related to the COVID-19 pandemic), especially for treatment with potential long-term or disease-modification effect.

ICE, intercurrent events; PO, potential outcome

Use a mix of strategies in handling ICEs in a study (Qu et al., 2020; Darken, 2020)

- One common drawback in most current clinical studies is that only ONE strategy is used to handle all ICEs
- Strategies for handling ICEs should be based on the underlying reasons
 - ICEs due to AE
 - AE at “normal time”
 - AE of COVID-19 illness
 - ICEs due to lack of efficacy (LoE)
 - Treatment discontinuation due to LoE
 - Use of rescue medication due to LoE
 - ICEs due to administrative reasons
 - Relocation, family situation changed, COVID-19 controlled measures, etc.

ICE, intercurrent events

Missing values

- Missing values
 - As a result of handling ICEs with hypothetical strategies
 - *True* missing values due to data not being collected
- Assumptions for missingness and methods to handle missing values should be based on the underlying reasons of ICEs or missingness
 - ICEs due to AE
 - AE at “normal circumstances”
 - AE of COVID-19 illness
 - ICEs due to LoE
 - ICEs due to administrative reasons

AE, adverse event; ICE, intercurrent events; LoE, lack of efficacy

Classification of Missingness

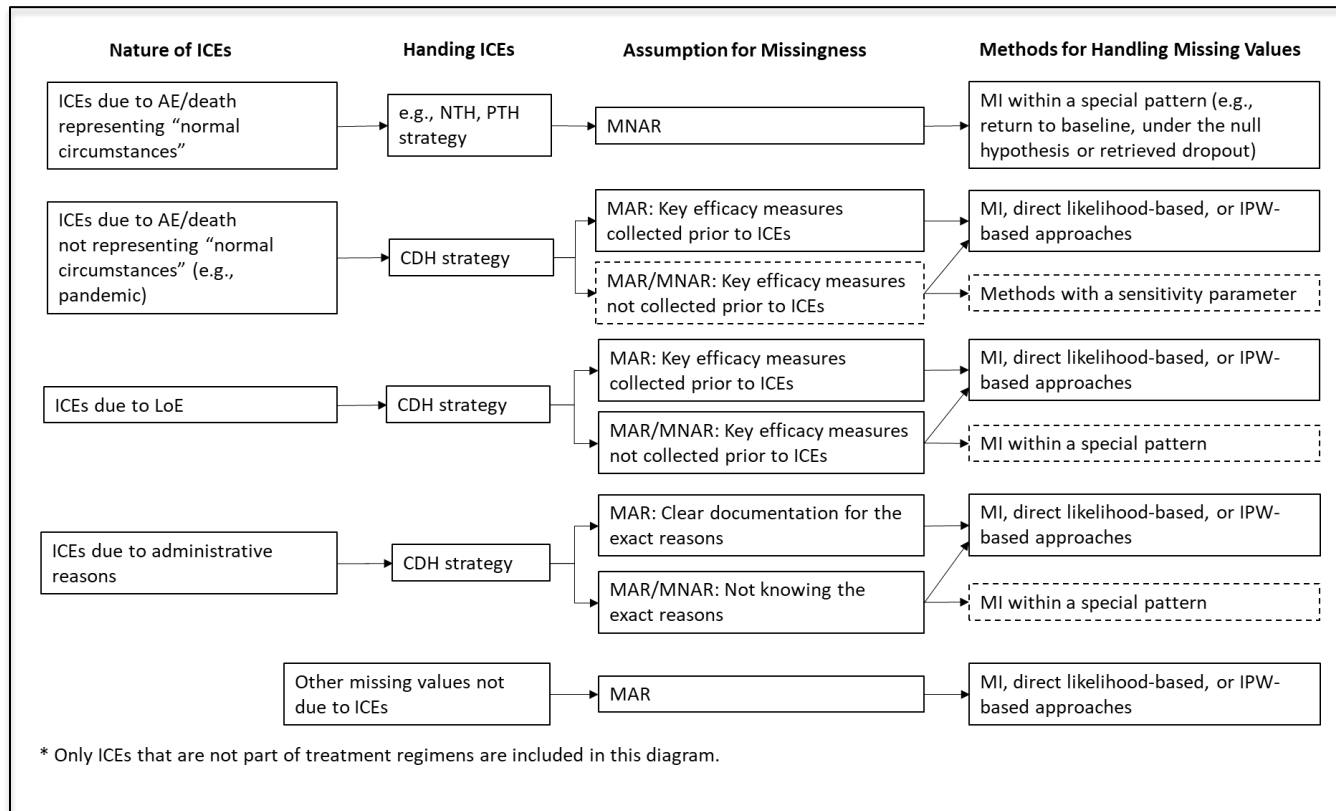
- In the context of a longitudinal clinical trial, missingness can be classified into four categories (Rubin, 1987; Little, 1995):
 - Missing not at random (MNAR). Conditional on the observed values, the probability of missingness is dependent of unobserved (missing) outcomes.
 - Missing at random (MAR). Conditional on the observed values, the probability of missingness is independent of any unobserved outcomes.
 - Covariate dependent MAR (Cov-MAR). Conditional on the baseline covariates, the probability of missingness is independent of any observed or unobserved outcomes (including treatment assignment).
 - Missing completely at random (MCAR). The probability of missingness is independent of any observed and unobserved variables.
- MCAR and Cov-MAR are special cases of MAR

Imputation or direct likelihood-based method in handling missing values

- MAR
 - Multiple imputation using patients in the same treatment group
 - Direct likelihood-based method, e.g., mixed model for repeated measures (MMRM)
 - Inverse probability weighing (IPW) based on the probability of missingness
- MNAR
 - Multiple imputation under a special pattern, e.g., reference-based imputation
 - Direct likelihood-based methods
 - Incorporating sensitivity parameters within multiple imputation-based or direct likelihood-based methods

MAR, missing at random; MNAR, missing not at random

Handling ICEs and missing values according to the nature of ICE/missingness



AE, adverse event
 CDH, controlled direct
 hypothetical
 ICE, intercurrent events
 IPW, inverse probability
 weighting
 LoE, lack of efficacy;
 MAR, missing at random
 MI, multiple imputation
 MNAR, missing not at random
 NTH, no treatment
 hypothetical
 PTH, partial treatment
 hypothetical

CHMP: Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (draft)

- “... Specifically, since patients are not expected to benefit once treatment is discontinued (e.g. due to adverse events) the treatment effect should be estimated based on observed or modelled data reflecting adherence to treatment as observed in the clinical trial.” **PTH or NTH strategy**
- “... Therefore, the treatment effect can be estimated under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario), provided that a reliable estimate of that effect can be obtained.” **CDH strategy**

An example – a study for heart failure indication

- The primary endpoint is the 6-minute walk distance (6MWD)
- The interest is the average of
 - Worst benefit for those who die
 - No additional benefit from the time of treatment discontinuation for patients who discontinue treatment due to AE (PTH)
 - Hypothetical treatment effect otherwise (CDH)

Intercurrent events	Estimand	Missing value	Estimation (handling the resulting missing values)
Death	Worst outcome (hypothetical)	Yes	Impute as 0
Treatment discontinuation due to AE	No benefit (hypothetical)	If no measurement collected at study end	MI under a special pattern - “Retrieved dropout” imputation
Treatment discontinuation due to other reasons	Hypothetical	Yes (as a result of censoring)	MI using patients in the same treatment group (MAR)
		Missing measurements due to being unable to perform the 6MWD test	Impute as 0
		Other missing measurements (e.g., due to COVID-19 controlled measures)	MI using patients in the same treatment group (MAR)

MAR, missing at random; MI, multiple imputation

Summary and Recommendations

- **Describing estimands**
 - Using PO language may help define and communicate estimands more succinctly. It also helps evaluate the plausibility of certain strategies for handling ICEs.
- **Defining endpoint**
 - For a composite endpoint, each component should be explicitly specified.
- **Defining ICEs**
 - Prior to discussing ICEs, treatment regimens of interest need to be defined precisely.
 - To be considered an ICE, this event should be a deviation from the treatment regimens of interest.
- **Handling ICEs**
 - Hypothetical strategies should be predominately used to define causal estimands.
 - Using a mix of strategies for handling ICEs is often clinically relevant.
- **Estimation**
 - Multiple imputation is a flexible tool allowing for implementing a mix of strategies to handle ICEs
 - Use the most *plausible* assumptions (not the most conservative assumptions)

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Thank you!

Q & A