STATISTICAL CONSIDERATIONS FOR CLINICAL TRIALS IMPACTED BY COVID-19

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on behalf of the Pharmaceutical Industry COVID-19 Biostatistics Working Group

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Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

R. Daniel Meyer, Bohdana Ratitch, Marcel Wolbers, Olga Marchenko, Hui Quan, Daniel Li, ...show all

Received 29 Apr 2020, Accepted 01 Jun 2020, Accepted author version posted online: 08 Jun 2020

Comment on: Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

Sylva H. Collins & Mark S. Levenson

Received 13 May 2020, Accepted 01 Jun 2020, Accepted author version posted online: 08 Jun 2020

Under a black cloud glimpsing a silver lining: Comment on Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic

Rob Hemmings

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- Key dimensions of pandemic-related factors, impacts, risk assessment, mitigations, and documentation
- Implications and mitigations for estimands
- Implications and mitigations for analysis: efficacy and safety analyses, missing data, sensitivity and supplementary analyses
- Considerations for study power and probability of success
- Considerations for the DMC and interim analyses

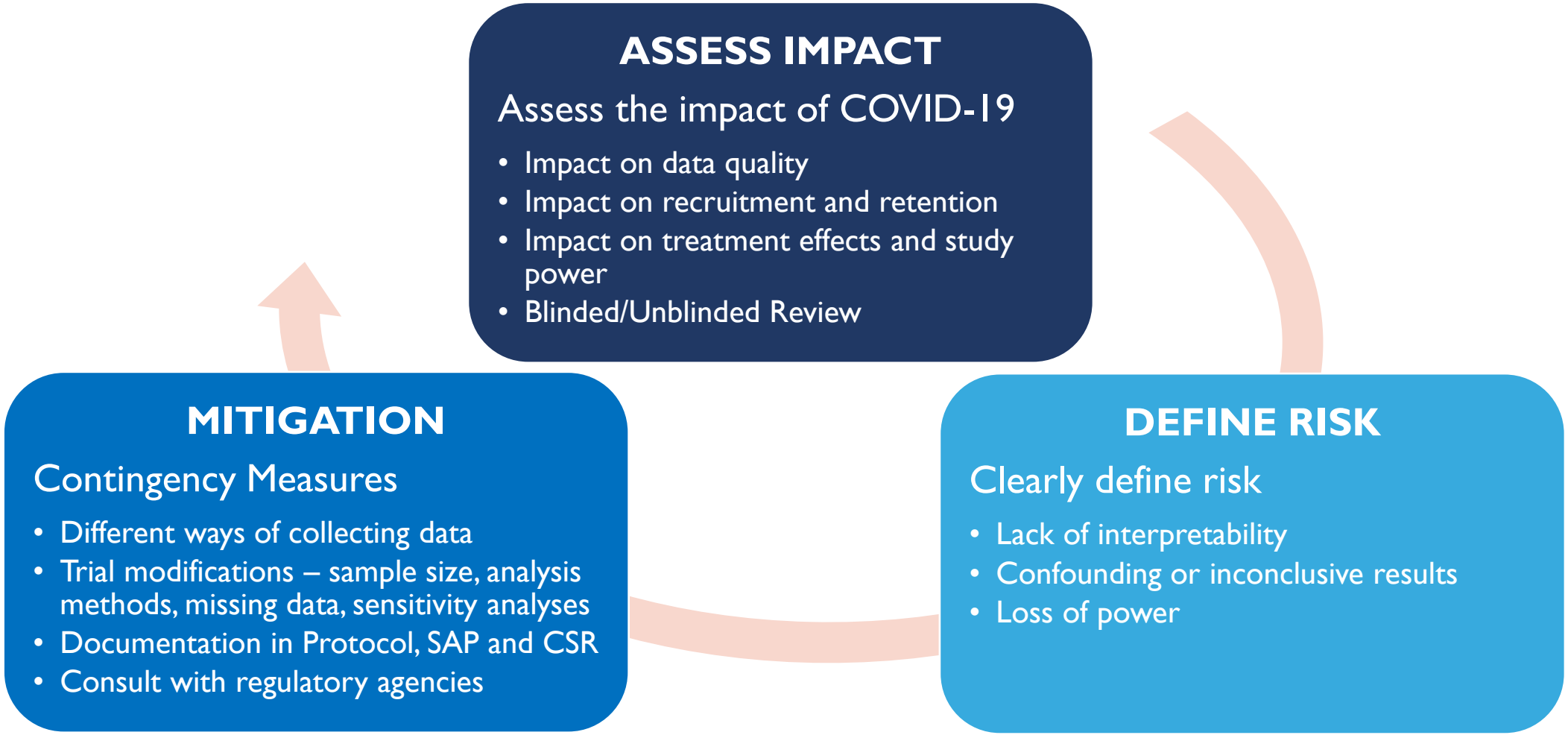
Outline

- Assessing Impact of COVID-19 on statistical design and analyses
- Accounting for pandemic impacts using the estimand framework
- Strategies for pandemic-related missing and unobservable values
- Sensitivity and supplementary analyses
- DMC and Interim Analysis considerations
- Summary
- References

COVID-19-related factors that are likely to impact ongoing trials

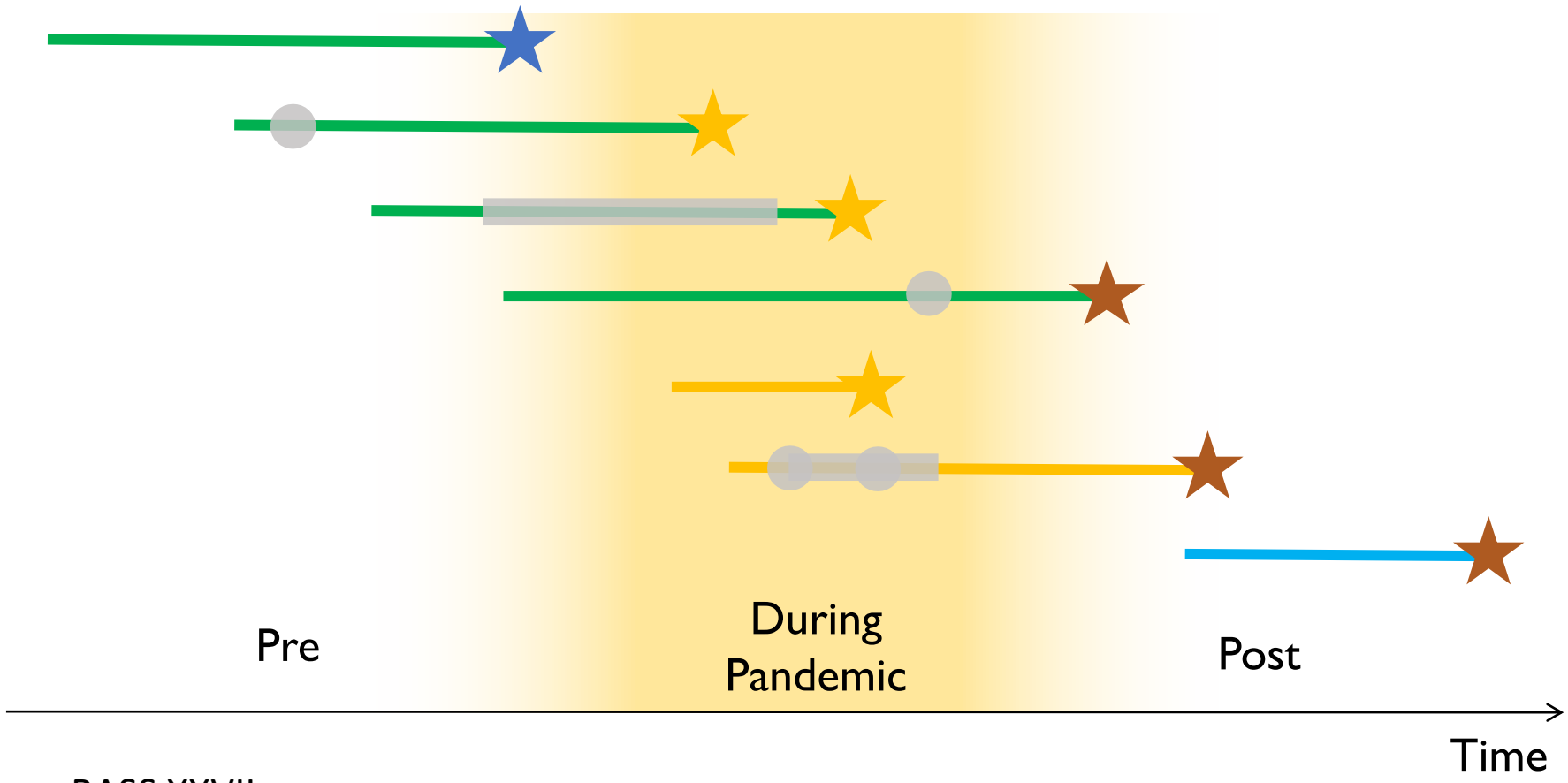
Factor	Example of Impact/ Risk
Quarantines, travel limitations, site closures or reduced availability of site staff	• Missed or delayed visits and assessments • Inability to access study treatment • Loss to follow-up • Longer query response time • Different investigators / different measurement modalities • Delayed site monitoring • Delayed patient enrolment
Interruptions to supply chain of experimental drug and/or other medications	• Missed dosing of study drugs • Changes in non-COVID-19 concomitant medications
Temporarily stopping drug due to safety concerns	• Informative censoring
Alternative administration of drug	• Increased risk of dosing errors • Equivalence of methods of administration
Alternative collection of specimens	• Reconciliation and verification
Alternative data collection	• Exchangeability of methods
COVID-19 infection / treatment	• Temporary/permanent interruption of study treatment and/or study participation • Potential effect on efficacy endpoints /estimands / safety • IMP interaction

Key steps to assess, define and understand the impact of COVID-19 on study and data integrity



How COVID-19 impacts ongoing clinical trials

Potential individual subject courses:



Readout/Dropout/Censor

Pre

During

Post

Enrollment period

Pre

During

Post

Interruption

Missed visit

Post pandemic?

- The SARS-CoV-2 virus will continue to circulate
- The initial shock to the healthcare system and impact of strict lockdowns will hopefully be behind us
- Difficult to identify clear boundary for post-pandemic era, but not difficult to envision future clinical settings:
  - Access to medical care resumes to pre-pandemic level
  - COVID-19 infections and complications reduces to non-pandemic level with effective vaccination and therapeutic options

Study objectives: staying the course in the face of pandemic

- Studies designed prior to the global COVID-19 pandemic, and most new studies not testing treatment for COVID-19, are meant to investigate the effect of treatments in the absence of the pandemic.
- "Ignoring" pandemic-related impacts in data collection and analysis may result in estimating a treatment effect confounded by pandemic-related factors.
  - » Inference may not align with the original scientific question
  - » Study conclusions may not generalize to post-pandemic clinical care
- Primary study objectives should continue targeting treatment effects free of confounding by COVID-19 pandemic factors.
  - » How do we account for the pandemic-related disruptions yet remain consistent with the study objectives?
- In some therapeutic areas, new exploratory objectives focused on specific COVID-19 related subpopulations, conditions, or drug-drug interactions may be of interest.

A motivating example

- Imagine a Phase III study of an experimental treatment as an add-on to a standard background therapy in patients with moderate/severe Chronic Obstructive Pulmonary Disease (COPD)
- Long-term symptom control (over one year) needs to be demonstrated

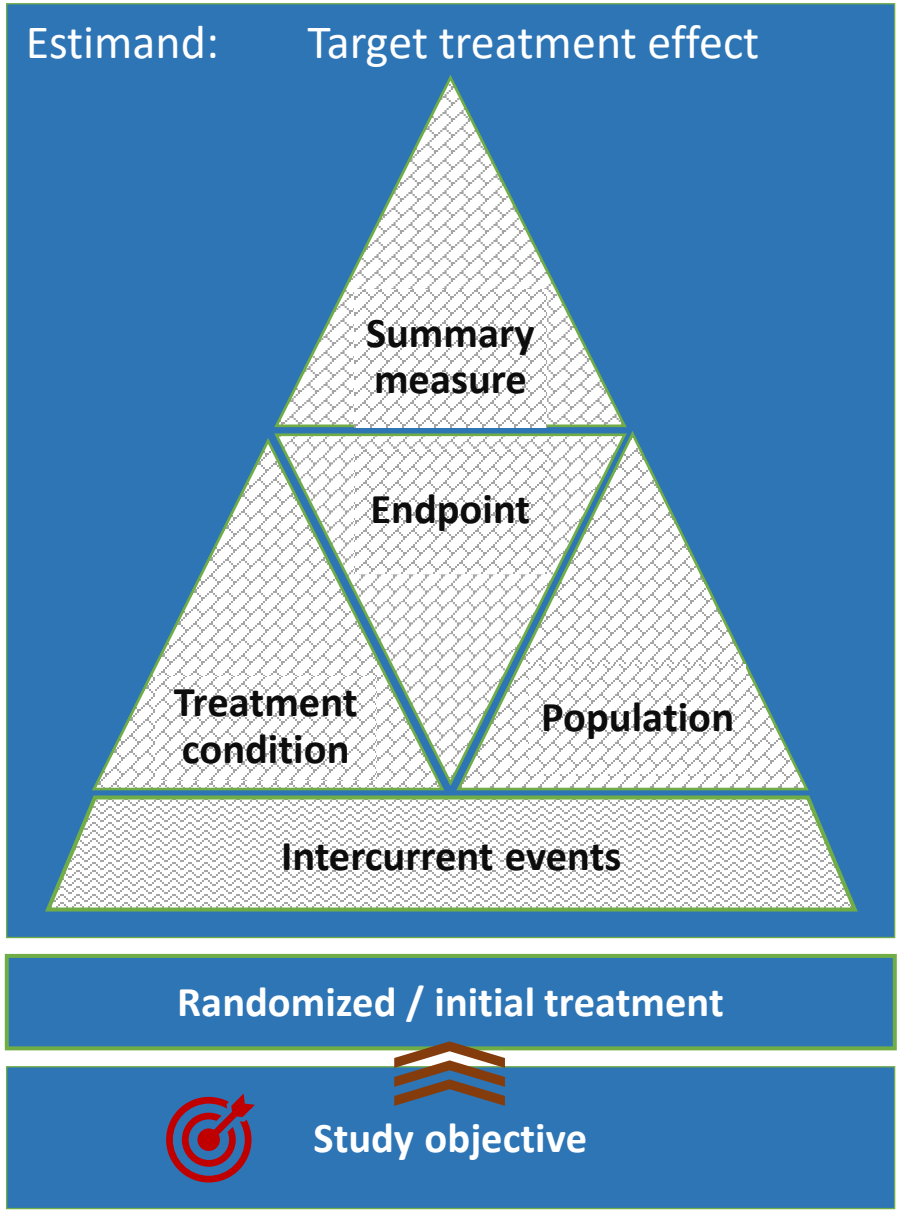
Plan before the pandemic

- It was anticipated that most study treatment discontinuations would be due to treatment-related reasons (lack of efficacy or toxicity).
- There are no effective treatment alternatives for participants who discontinue randomized treatment prematurely - expected to remain on the background therapy only.
- Effect of incomplete treatment on the endpoint measured over one year is of interest.
- Therefore, all treatment discontinuations were planned to be addressed using the treatment policy strategy.

Reality during the pandemic

- In the context of COVID-19 pandemic, participants may also discontinue study treatment due to:
  - Site operation disruptions
  - Participant's perception of increased risk versus benefit from the study participation
- Complications of COVID-19 infection and start of COVID-19 therapy in a hospital setting
- COVID-19 death
- Doesn't make sense to use the treatment policy strategy for all COVID-19 related intercurrent events.

Estimand framework – A helpful Tool



- Estimand framework as the means to detail the study objective and define targeted treatment effect using five attributes.
- COVID-19 pandemic disruptions may impact the estimated treatment effect, with impact potentially exerted via any of the five estimand attributes

- Study treatment interruptions
- Alternative methods of assessment
- COVID-19 hospitalizations, therapies, deaths

If estimands were not formally defined, still useful to assess the impacts systematically and as basis for regulatory discussions

Intercurrent Events (ICE)

- The same type of intercurrent events (e.g. treatment discontinuations, deaths) may be COVID or non-COVID related, even during the pandemic.
- Accurate identification of COVID-19 pandemic-induced intercurrent events is a challenging task
  - Correct coding of COVID-19 adverse events and diagnoses in the database
  - Dedicated eCRF entry or standardized language to capture COVID-19 related protocol deviations
  - Query of suspected cases based on medical monitoring

Strategies for ICE

General considerations with exceptions for specific disease areas and populations:

- Treatment policy

  In many cases, clinical outcomes after pandemic-related ICEs would not be of interest with respect to the original study objective(s), and conclusions would not generalize to clinical care in "post-pandemic world" .

- Composite

  ICEs due to pandemic-related reasons (e.g., disruptions with study treatment availability) usually cannot be interpreted as evidence of study treatment effectiveness or tolerability.

- Hypothetical
  - a natural choice for pandemic-related study treatment discontinuations in many settings, with the hypothetical scenario "if participant did not discontinue study treatment".
  - It may be considered for ICE of COVID-19 death, with the hypothetical scenario "if participant did not die", in disease areas with minimal mortality where death is not a component of the endpoint.

Missing and unobserved data

- Despite best efforts, sponsors should prepare for the possibility of increased amounts and/or distinct patterns of missing data.
- Missingness is not an ICE in itself.
- Missingness may or may not occur with an ICE.
- Target outcomes are unobservable under hypothetical scenarios.

Missing and unobservable data

ICE occurred

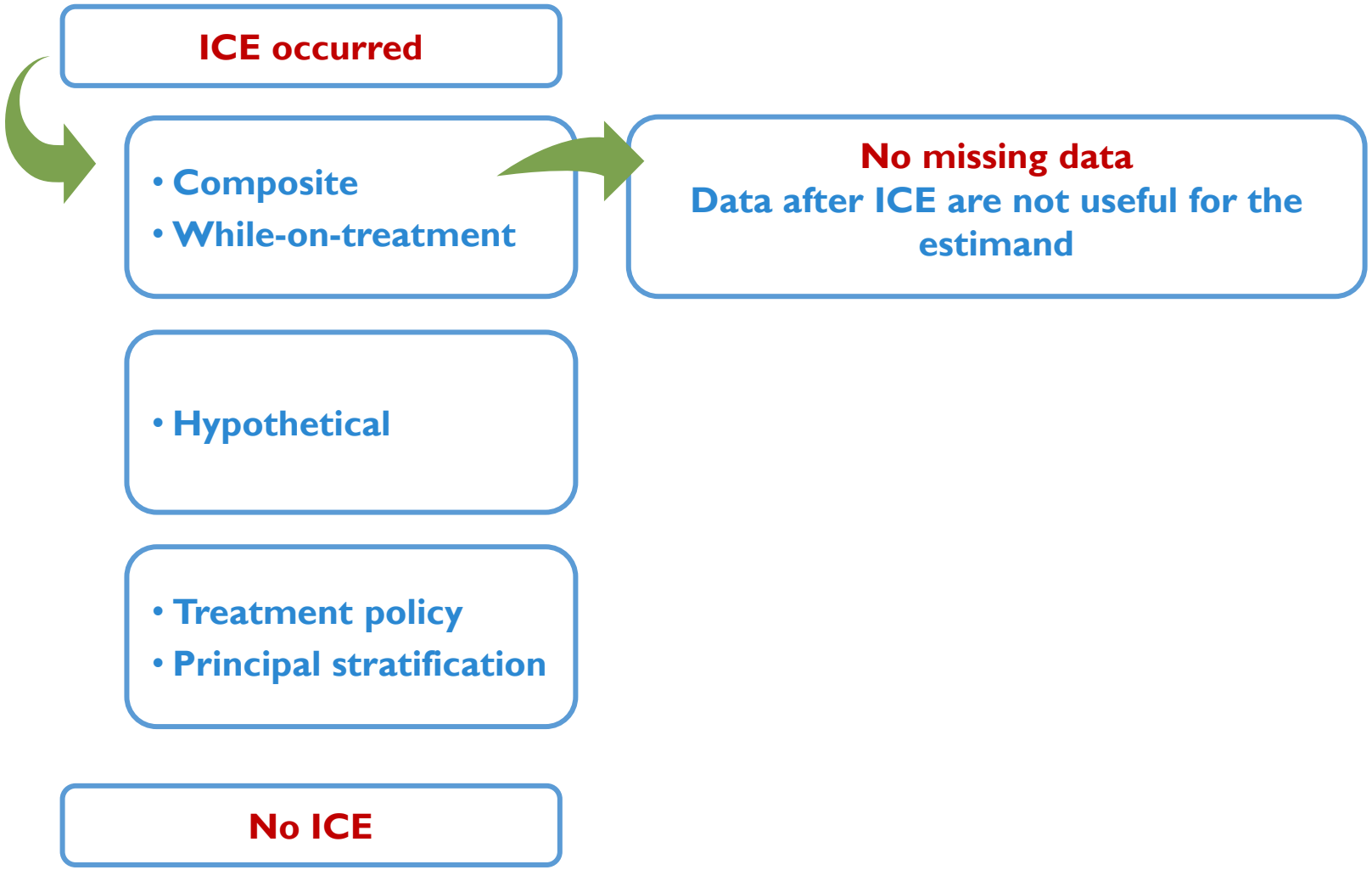
- **Composite**
- **While-on-treatment**

- **Hypothetical**

- **Treatment policy**
- **Principal stratification**

No ICE

Missing and unobservable data



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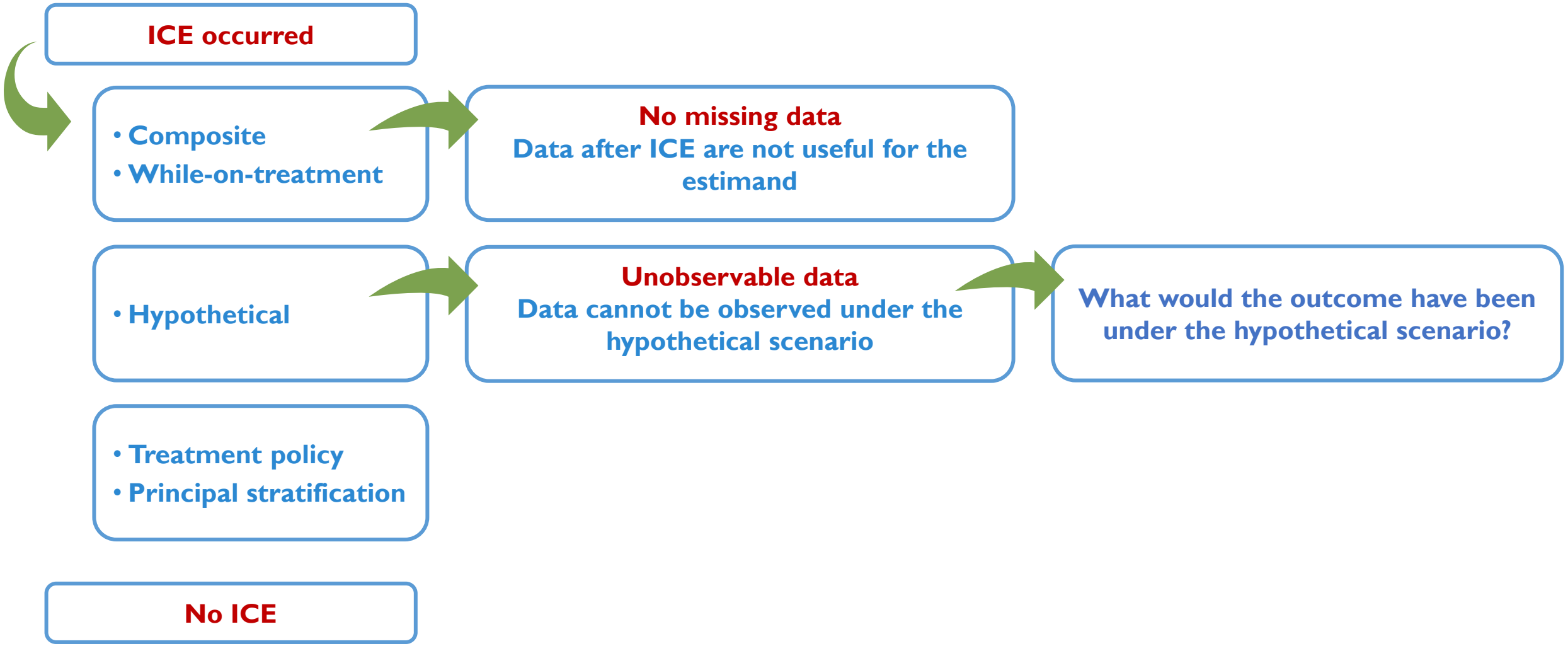
Missing and unobservable data



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Missing and unobservable data

ICE occurred

- **Composite**
- **While-on-treatment**

→ **No missing data**
Data after ICE are not useful for the estimand

- **Hypothetical**

→ **Unobservable data**
Data cannot be observed under the hypothetical scenario

→ **What would the outcome have been under the hypothetical scenario?**

- **Treatment policy**
- **Principal stratification**

→ **Missing data**
Data would have been appropriate for the estimand but not available

- Missed assessment
- Incomplete assessments
- Delayed, out-of-window assessment
- Withdrawal from study

→ **What would the outcome have been given the nature of the ICE and estimand strategy?**

No ICE

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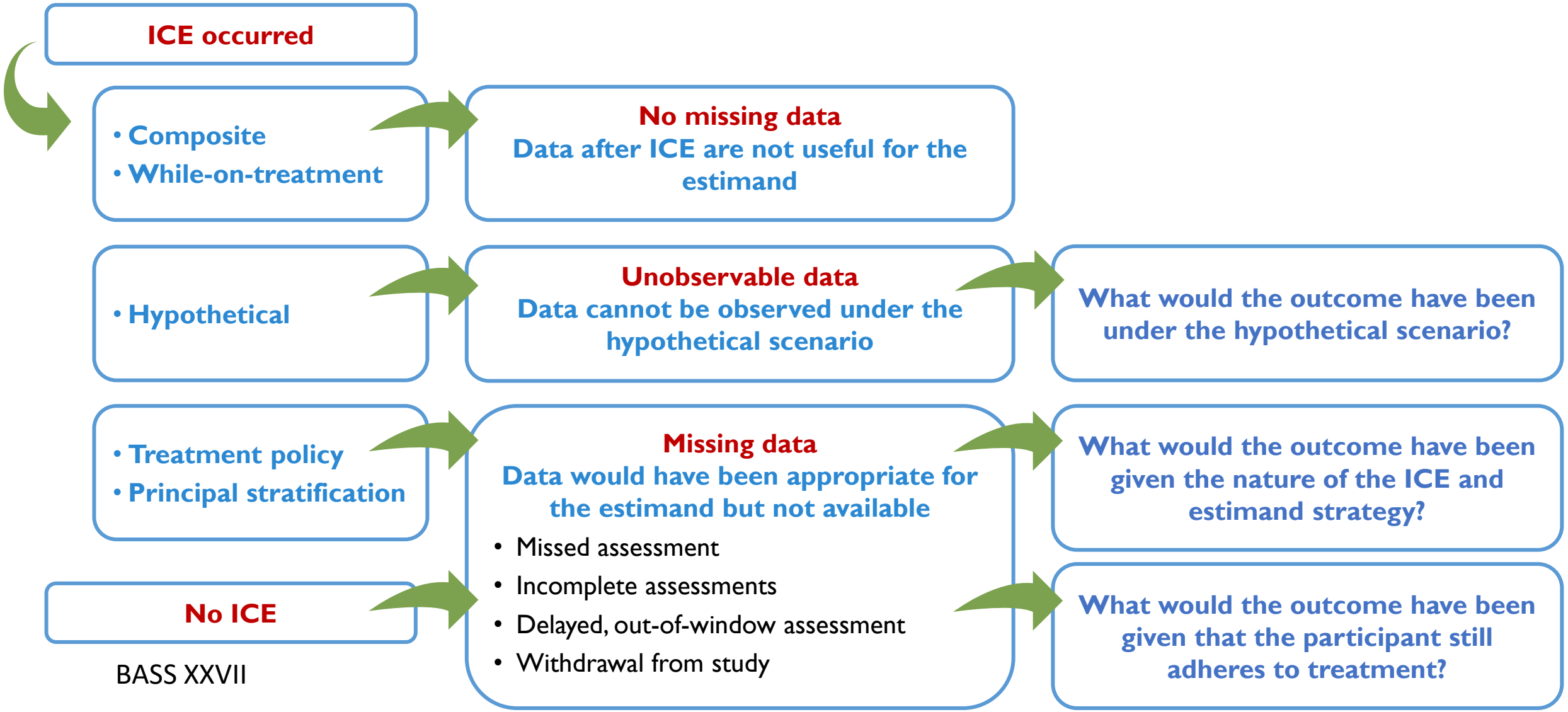
Missing and unobservable data



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Pandemic-related factors and missingness mechanism

Reasons for missing / unobservable values could be pandemic-related or not (see factors discussed for ICEs)

Pandemic-related factors

- Structural, e.g., government enforced closures or sites stopping study-related activities
- Participant-specific, e.g.,
  - Individual concerns for COVID-19 or individual COVID-19 infection and complications
  - Participants with milder disease or lower treatment response may be more inclined to discontinue the study

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Missingness mechanism

- Missing Completely at Random (MCAR): probability of missingness is independent of all participant-related factors or, conditional on pre-randomization covariates, the probability of missingness does not depend on either the observed or unobserved outcomes.
- Missing at Random (MAR): conditional on pre-randomization covariates and observed outcomes, probability of missingness does not depend on unobserved outcomes.
- Missing Not at Random (MNAR): probability of missingness depends on unobserved study outcomes.

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- Implication of MCAR / MAR is that missing values can be modelled based on available data from "similar" participants.

Pandemic-related factors and missingness mechanism

Reasons for missing / unobservable values could be pandemic-related or not (see factors discussed for ICEs)

Pandemic-related factors

- Structural, e.g., government enforced closures or sites stopping study-related activities
  - » Can be considered MCAR
- Participant-specific, e.g.,
  - » Individual concerns for COVID-19 or individual COVID-19 infection and complications
  - » Participants with milder disease or lower treatment response may be more inclined to discontinue the study
  - » If reasons for missingness, ICEs, relevant covariates and early outcomes are captured, may often be considered MAR
  - » Sometimes, may need to be modeled under MNAR

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Strategies for pandemic-related missing and unobservable data

Model / impute

Include participants in the analysis set with partial data

Many methods are readily available, e.g.:

MCAR or MAR

- Direct likelihood, e.g., mixed models for repeated measures (MMRM)
- Generalized linear (mixed) models
- Cox proportional hazards regression

MNAR

- Pattern-mixture model framework
- Selection model framework
- Shared parameter model framework

Multiple imputation can be useful to impute missing values when

- A direct likelihood method cannot be used;
- Imputation model needs to adjust for auxiliary covariates;
- Imputation model needs to be estimated from a specific reference group (subset) and/or with deviations from MAR

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Exclude

Exclude participants from the analysis set

MCAR

- May be considered for data missing/unobservable due to structural reasons if available data for affected participants at a site would contribute little or no information about the treatment effect
- To avoid bias, exclude all participants at a given site who would have had endpoint assessment during disruptions period, regardless of post-randomization outcomes (see FDA, 2020 guidance)

When MAR may be appropriate

Context

- Participant in a Rheumatoid Arthritis (RA) study was unwilling to come to the clinic for study visits during the pandemic, discontinued study treatment, and withdrew from the study.
- The ICE is planned to be addressed by a hypothetical strategy under the scenario "if participant has not discontinued study treatment at that time".

Considerations and strategy for handling missing values

- Participant's discontinuation is not related to treatment or disease outcomes and is pandemic related.
- Unobserved outcomes could be modelled based on other participants who remained in the study.
- Participant's age may be related to both decision to discontinue treatment and to RA outcomes.
- The primary endpoint is binary.
- Multiple imputation can be used with an auxiliary covariate of age, while keeping the analysis model as originally planned.

When MAR may not be appropriate: Example of missing data under treatment policy strategy

Context

- Participant in a COPD study discontinued treatment due to an AE.
- The ICE is planned to be addressed with the treatment policy strategy.
- After the start of the pandemic, participant withdraws from the study, which results in missing data.
- Reason for study withdrawal: participant's condition deteriorated and they are worried that clinic visits would increase their risks associated with COVID-19.

Consideration and strategy for handling missing values

- Pre-discontinuation efficacy outcomes may have been favorable, but would be expected to worsen after treatment discontinuation.
- Worsened outcomes are not fully captured and may be more severe than in participants who remained in the study.
- An MNAR approach could assume worse outcomes than what would be predicted by a model estimated from participants who discontinued study treatment but remained in the study (see e.g., the "attributable estimand approach" in Darken et al., 2020).
- The extent of "worse" should be clinically plausible and investigated in sensitivity analyses, e.g., tipping point.

When MAR may not be appropriate: Example of unobservable data under hypothetical strategy

Context

- A heart disease study is using a primary endpoint of time to MACE endpoint.
- Participant discontinued study treatment due to hospitalization and initiation of an experimental treatment for COVID-19.
- Participant survived COVID-19 but withdrew from the study without experiencing any MACE.
- The ICE is planned to be addressed by a hypothetical strategy under the scenario "if participant has not discontinued study treatment at that time".

Considerations and strategy for handling unobservable values

- As the study disease may be a risk factor for COVID-19 complications, the participant might have had a more severe heart disease than participants in the study who did not experience severe complications of COVID-19.
- Time-to-event models do not typically include post-randomization outcomes and adjust for a limited set of baseline covariates, if any.
- Modeling unobservable outcome with an ignorable censoring model from participants remaining in the study may not be appropriate.
- An MNAR approach could assume that the hazard of MACE is higher for this participant, quantified by a sensitivity parameter.

When MAR may not be appropriate: Example for missing data with no ICE

Context

- Participant in a Generalized Anxiety Disorder (GAD) study continued taking the study treatment as planned through the end of study.
- Participant has not attended the clinic to complete the primary assessments after the start of pandemic.

Considerations and strategy for handling missing values

- The fact that the assessments have not been completed may indicate that participant's GAD worsened after the pandemic start.
- Modeling missing data under MAR based on other patients in the study who continued adhering to treatment and completed assessments may not be appropriate.
- An MNAR approach could assume that the missing values of this participant would be similar to the worst quartile of participants with available data who were in the study during the pandemic lockdown.

Examples of estimand and analysis strategies for study treatment discontinuations

ICE: Discontinuation of study treatment due to ….		Migraine prevention study	Generalized Anxiety Disorder study	COPD study
… site operation disruptions	Estimand strategy:	Hypothetical "if participant did not discontinue study drug at that time"		
	Analysis strategy:	Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.*		
… participant's perception of increased risk versus benefit from the study	Estimand strategy:	Hypothetical "if participant did not discontinue study drug at that time"		
	Analysis strategy:	Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.*	Predict outcome under the assumption of lower than average treatment effect in similar participants who did not discontinue.	
… severe complications of COVID-19 infection and start of COVID-19 therapy	Estimand strategy:	Hypothetical "if participant did not discontinue study drug at that time"		Composite strategy as an unfavorable outcome
	Analysis strategy:	Predict outcome under the assumption that it would be similar to participants who did not discontinue, adjusting for relevant covariates.*		Count as endpoint event or designate an unfavorable endpoint value

*This includes possibility of discontinuing later due to non-pandemic related reasons.

Feasibility considerations for estimation with missing / unobservable data

- Missing / unobservable outcomes are often modelled based on data from other "similar" participants with observed data, possibly with some additional assumptions.
- It is, therefore, important to ensure that the observed data and chosen models are adequate for predicting (implicitly or explicitly) the missing and unobserved outcomes / treatment effect.

Feasibility considerations for estimation with missing / unobservable data

- Questions to be considered:
  - Are reasons and contributing factors for the ICEs and missed assessments well documented for proper attribution?
  - Are there adequate observed data in participants whose characteristics overlap with characteristics of participants with missing / unobserved data to minimize extrapolation?
  - Does the predictive model have a good fit, predictive accuracy, and/or leads to robust inference?
  - Is there sufficient understanding of expected disease trajectories or external data to check plausibility of imputations and/or to make additional assumptions?
  - What is the effect of the amount of missing / unobserved data on statistical power?
- If such questions are part of risk assessment and mitigation, favorable answers to these questions should be feasible in most trials.

Tools for feasibility / robustness assessments

- Compare characteristics of participants with missing/unobservable data and those with observed data.
  - » Examine demographic, disease characteristics, known and suspected risk factors, early outcomes.
  - » Use plots, summary statistics; consider positivity and overlap concepts from causal inference.
- Check plausibility of imputed values based on clinical disease understanding and external data.
  - » Use historical and/or RW data to inform assumptions.
  - » Use baseline and/or placebo distributions to characterize limiting scenarios.
- Compare distribution of observed and imputed data, conditional on the propensity of being observed.
- Examine standard regression and influence diagnostics for the imputation and analysis model.
- Use leave-one-out cross-validation to assess predictive accuracy by strata based on missingness propensity.
- Use Bayesian posterior predictive checking to check robustness of inference.

(See e.g., Nguyen et al. 2017; Polverejan & Dragalin, 2019)

Sensitivity and supplementary analyses

Sensitivity and supplementary analyses may help assess the impact of pandemic-related disruptions:

- Delayed/out-of-window assessments, missing data
- Alternatives to Protocol-specified data collections
- General pandemic impact on trial outcomes

Delayed assessments and missing data

- Visits may be delayed due to site closure or travel restrictions. Treating out-of-schedule visits as missing data may be a type of sensitivity analysis
- For missing data due to pandemic-related interruptions
  - Tipping point analysis (Ratitch, O'Kelly and Tosiello 2013) may be used to assess the degree of departure from missing data assumptions to overturn conclusion of primary analysis
  - Extended set of variables for imputation algorithm when primary analysis relies on imputation techniques
  - Varying assumed probabilities of potential treatment adherence for missing data with ICE handled with hypothetical strategy
  - Interval-censored methods for time-to-event endpoints with skipped visit/imaging scans due to pandemic

Alternatives to protocol-specified data collection modalities

- Exchangeability of alternative needs to be assessed.
  - External validation
  - Blinded data comparisons between modalities
- Sensitivity analysis regarding alternative modalities of data collections
  - Include only data collected according to the original protocol and treat other modalities as missing
  - Modeling the interaction of between treatment and assessment methods
  - Bayesian analysis “borrowing” information from alternative data modalities using power or hierarchical priors

General pandemic effect on trial outcomes

- Other systematic difference may exist due to factors not captured in the clinical trial database
- Analyzing trial data by Pandemic time periods may be challenging
  - Rolling impact on different regions and sites
  - Patient journey during the trial may overlap with different pandemic periods (time-varying indicators?)
- Stratifying patients by the extend of pandemic impact
  - Treatment compliance
  - Pandemic-related ICEs
  - Missing assessments

Considerations for DMC

- We do not generally advocate the use of DMC for operational risk assessment/mitigation process, to prevent influence of unblinded data
  - DMC may request additional data presentations, including specific COVID-19 related reports to better monitor participant safety.
  - Blinded assessments of trial data and real-time operational feedback are typically sufficient to inform appropriate modification of the trial for pandemic-related risk mitigation
- DMC should be well-informed of all measures taken to protect participants safety and to address operational issues related to the pandemic.

Interim Analyses

Efficacy interim analyses should be conducted as planned with information level when feasible.

- In case with strong scientific rationale for a change in interim/final analysis timing when the information level becomes unreachable due to the pandemic, DMC should be informed and consulted
- Changes to estimand, planned analyses or decision rules due to pandemic-related disruptions should be communicated to DMC and documented in the charter or related analysis plan.

Summary

- The estimand framework provides a systematic pathway for assessing the impact of the pandemic.
- Pandemic-related intercurrent events will likely need to be defined to properly and rigorously account for unexpected pandemic effect.
- Most pandemic-related missing/unobserved data is likely MCAR or MAR, especially if missingness is due to structural reasons, but additional considerations may apply, especially for certain diseases and participant-specific missingness.
- Sensitivity and supplementary analyses are needed to assess both the specific aspects of the pandemic interruptions and the general impact
- Roles of DMC and sponsor for pandemic-related monitoring and risk assessment should be clarified to maintain the integrity of the trial and avoid operational bias.

References

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