COVID-19: Estimands to the rescue?

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Outline

1. Trial integrity and complications arising from the pandemic
2. Intercurrent events, estimands and the ICH E9 addendum
3. Estimands and the pandemic
4. Missing data considerations
5. Conclusions

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Trial integrity in view of the pandemic

- Data integrity is defined as the extent to which all trial data are complete, consistent, accurate, trustworthy, and reliable throughout the data lifecycle
- Trial integrity is a concept relating to trial conduct more broadly, which encompasses data integrity and which refers to the ability of a trial to produce results which are not affected by (unknown) biases, e.g.
  - Unblinding can result in a loss of trial integrity
  - Cohort effects and informative dropout mechanisms if unknown and not adequately accounted for can lead to a loss of trial integrity
- Extent to which trial integrity is affected has an impact on clinical trial interpretability and the conclusions that we can draw from the data collected
- COVID-19 pandemic related complications endanger trial integrity

Complications due to the pandemic

Complications due to administrative/ operational challenges

- treatment discontinuation due to drug supply issues;
- treatment discontinuation due to subject concerns;
- inability to perform important procedures (e.g. biopsies, laboratory / diagnostic tests);
- missed visits (e.g., subject preferences, self-isolation or government restrictions such as quarantines or lockdowns);
- visits outside of the designated time window;
- altered or compromised visits due to overloads of health system

Complications related to impact of COVID-19 or the pandemic on the health status

- treatment discontinuation due to COVID-19 symptoms;
- intake of additional meds to treat COVID-19 symptoms;
- death due to COVID-19;
- health issues induced or exacerbated by the government restrictions or the health system overload;
- inability of COVID-19 infected subjects to attend scheduled visits

Characteristics of these complications

- Unforeseen at design stage
- May be a direct consequence of measures taken because of the pandemic
- Often expected to apply similarly to different treatment arms
  - exceptions exist, e.g., open label trials or trials which contain immunosuppressive drugs
- Extent of the complications will likely vary
  - across different regions and sites, even within the same country
  - depending on attributes of the actual patients (the elderly and those with conditions such as asthma etc. are at higher risk of missing visits and adverse consequences from COVID-19)
- Some complicating events prevent relevant data being collected and result in a missing data problem
- Some of these events affect either the interpretation or the existence of the measurements associated with the clinical question of interest (intercurrent events)

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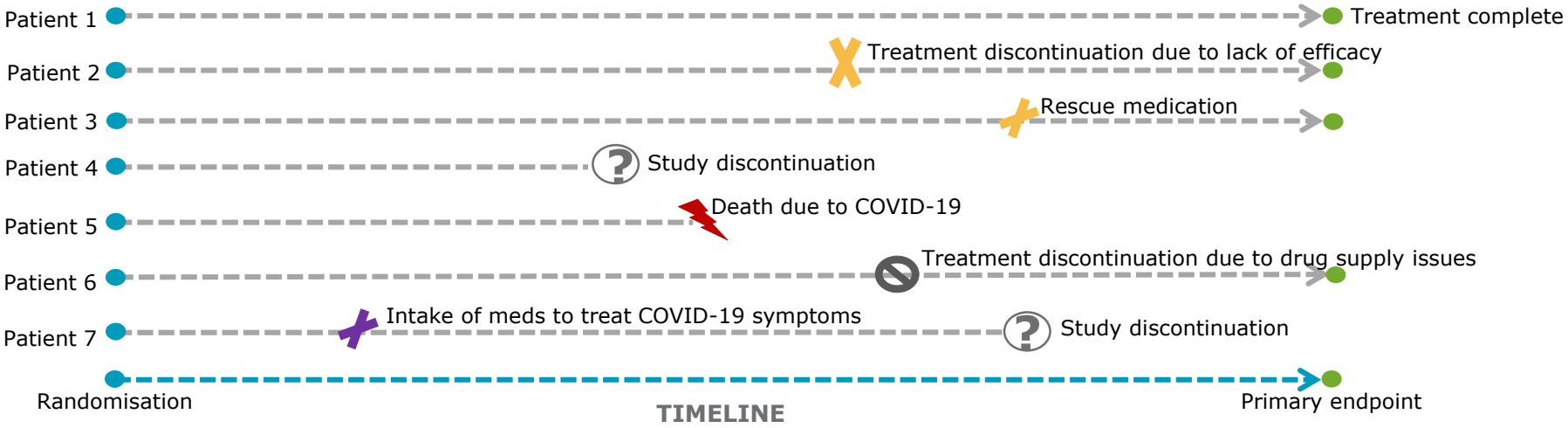
Intercurrent events

- Events that occur after randomization, e.g. study treatment discontinuation due to an adverse events, which affect either the interpretation or the existence of the measurements associated with the clinical question of interest



- Intercurrent events are at the heart of the ICH E9 addendum which was published earlier this year

‘Guiding star’ of pharmaceutical statistics

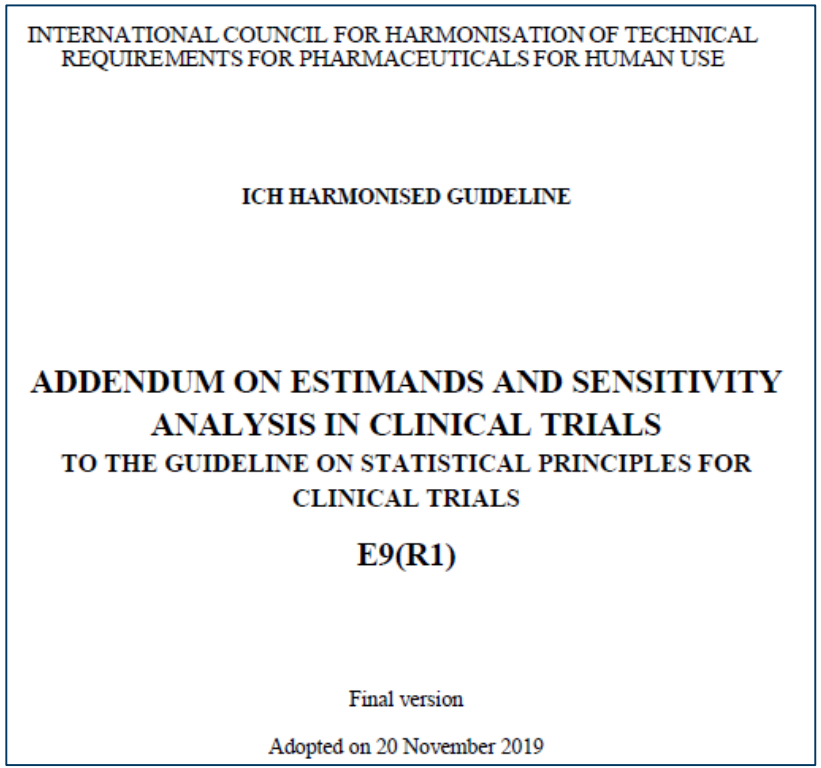
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998

Draft ICH E9 (R1) – the addendum



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

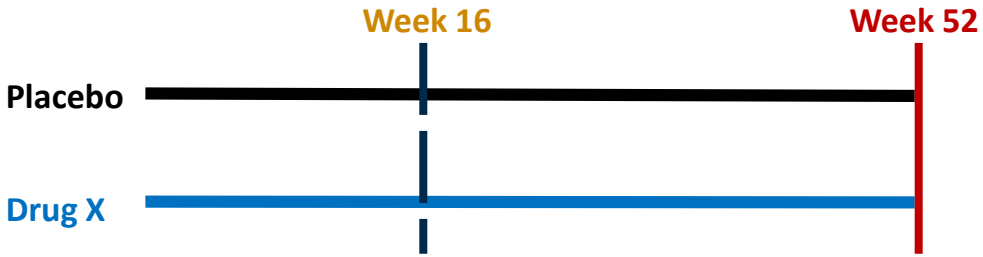
Adopted on 20 November 2019

So what is an estimand?

- Represents **WHAT** is most important to estimate in order to address the scientific question of interest
- An estimator represents **HOW** to estimate the estimand
- The revision of the ICH E9 was triggered by concerns that we often focus on the HOW rather than on the WHAT
  - The WHAT is sometimes implicitly driven by the HOW
- ICH E9 (R1) aims to re-assign primacy to the question we ask, not the methods by which we answer them (see also Sheiner (1991), Box (1976))
- ICH E9 (R1) introduces a new framework to better align the WHAT and the HOW

Clinical trial example for illustration

- Randomized, double-blind, placebo-controlled Phase III study
- Compare a biologic Drug X versus Placebo in the treatment of an inflammatory disease
- Clinical measurement of interest: continuous symptom score at week 52

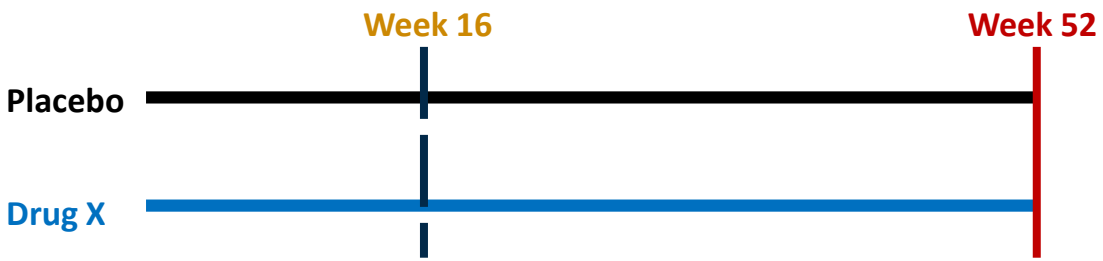


- **Patients are allowed to switch to rescue therapy (essentially Drug X itself) after week 16 if symptoms are not controlled**
- **Many Placebo patients are expected to switch to Drug X after week 16**
- **No deterministic rule for switching to rescue**
- **Patients are followed up beyond switching**

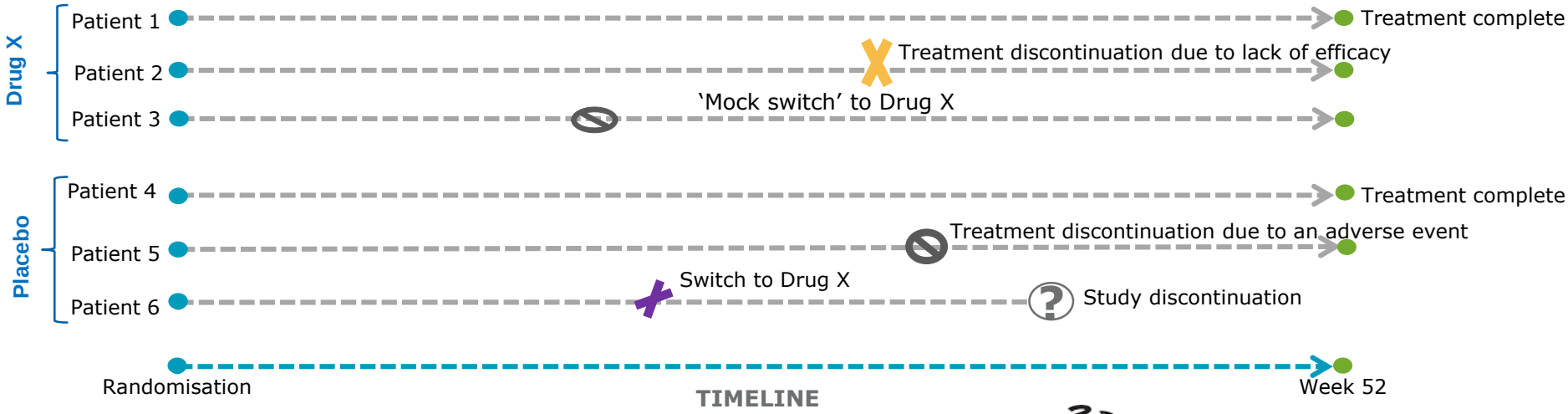
Trial objective

Objective according to the protocol:

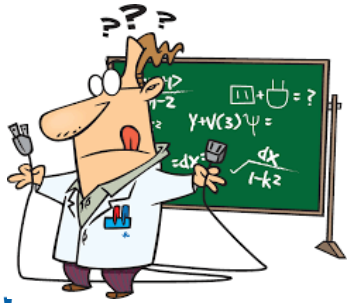
“To demonstrate that the efficacy of Drug X at Week 52 is superior to Placebo based on the change from baseline in the continuous symptom score.”



Is this objective precise enough?



These events are not captured in the objectives!



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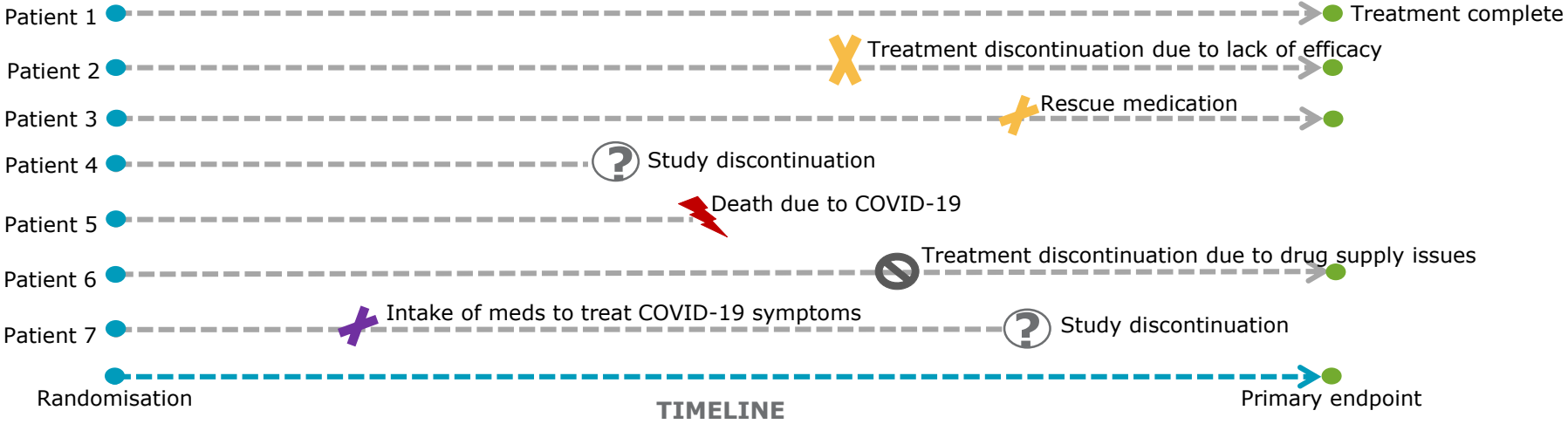
Objective leaves room for ambiguity on the estimand (the WHAT)

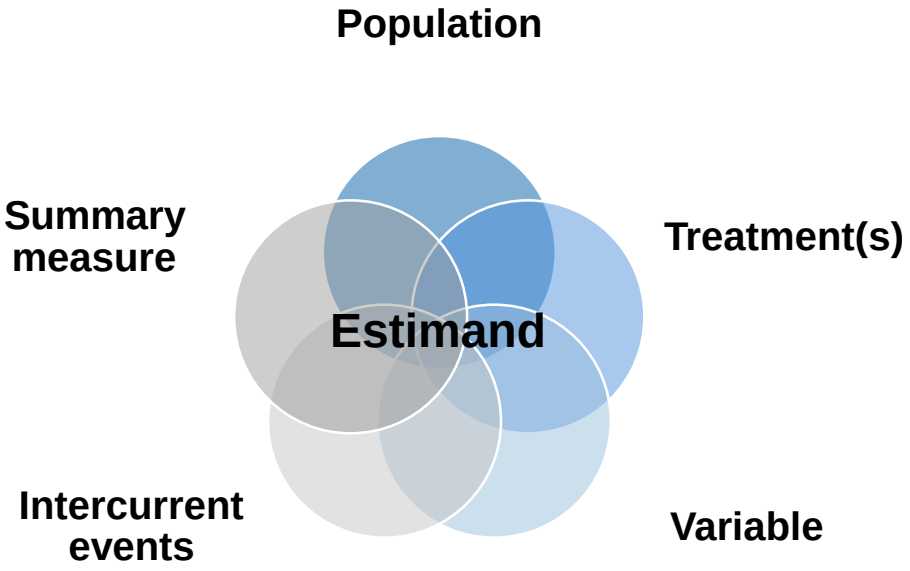
- Effect of assigning Drug X vs assigning Placebo, regardless of treatment switching and treatment discontinuation → Treatment policy
- Effect of Drug X vs Placebo if all patients remained on their randomized trt throughout 52 weeks → Hypothetical
- Effect of Drug X vs Placebo where patients that switch to rescue or discontinue trt are considered trt failures → Composite
- Effect of Drug X vs Placebo while patients did not switch to rescue or discontinue trt → While-on-treatment
- Effect of Drug X vs Placebo in patients that do not switch to rescue or discontinue trt in either treatment arms → Principal Strata

A lot of this boils down to:

- How do we account for events that occur after randomization?
- COVID-19 results in numerous unforeseen intercurrent events



Estimands



A thinking process…

1. Therapeutic setting and intent of treatment determining a trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices on trial design, data collection and method of estimation
6. Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7. Document the chosen estimands

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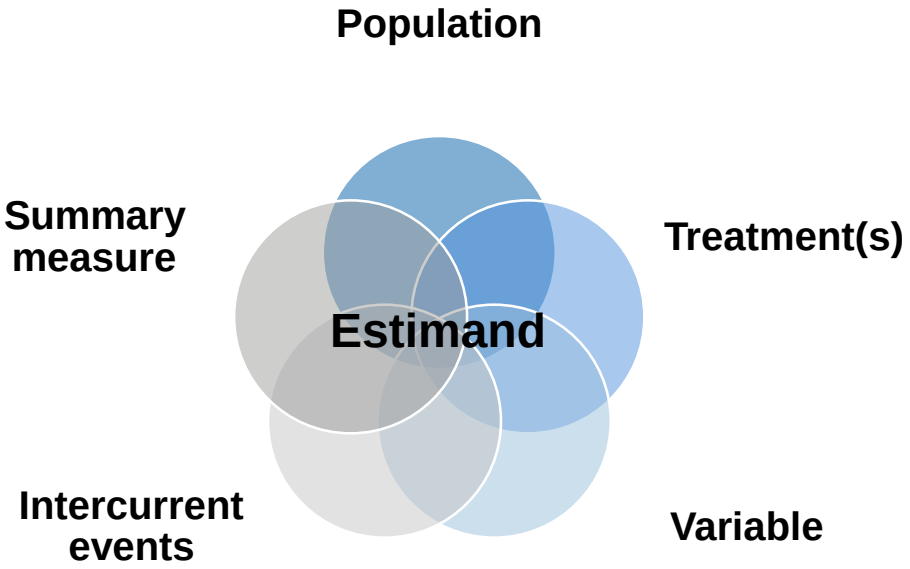
Estimand attributes are likely impacted by COVID-19 pandemic



Examples:

- **Population**: may need to adapt inclusion/exclusion criteria, e.g. exclude COVID-19 high-risk patients
- **Treatment(s)**: prohibit intake of anti-inflammatory background medications
- **Variable**: Change from week 52 endpoint to week 26 endpoint
- **Intercurrent events (ICE)**: additional unforeseen events occur, e.g. treatment interruption due to drug supply issues, death due to COVID-19, ...

Considerations on intercurrent events

- ICE related to pandemic neither foreseen nor addressed at the design stage
- ICE unrelated to pandemic were probably already foreseen at the design stage
- How to handle foreseen ICE such as ‘treatment discont. due to any reason’?
  - While foreseen at the design stage, pandemic-related reasons and frequency of occurrence were not anticipated
- It is recommended to distinguish between COVID-19 pandemic related and unrelated intercurrent events, e.g.
  - ‘treatment discont. due to drug supply issues caused by the pandemic’ versus ‘treatment discont. due to lack of efficacy’ versus ‘treatment discont. due to any reason’

Estimand considerations

- For pandemic-unrelated foreseen ICE there is likely no need for action
  - Changes in estimand w.r.t. foreseen ICE may be controversial & need justification
- Need to articulate the estimand of interest in respect of unforeseen ICE
  - No mention/adaptation implicitly suggests a treatment policy strategy, i.e. the effect regardless of the interecurrent events – this may be appropriate when only a few unforeseen ICE occur
  - If many unforeseen ICE occur, may want to discuss alternative choices
  - Do we need to distinguish between ICE related to operational challenges versus ICE related to health status of the patient?
  - In which cases is a hypothetical strategy more relevant?

Role of hypothetical strategie(s)

- Hypothetical question: What is the treatment effect in a world where the COVID-19 virus does not exist?
- Alternative hypothetical question: What is the treatment effect in a world where individuals can suffer from a COVID-19 infection but where the pandemic-related operational challenges do not occur?
- Hypothetical question(s) seem plausible for ICE related to operational challenges
- Relevance/acceptability is less clear for ICE related to health status, e.g. death due to COVID-19 in a CV outcome trial where death is an outcome of interest
  - Can we reliably estimate the hypothetical outcome with plausible assumptions?

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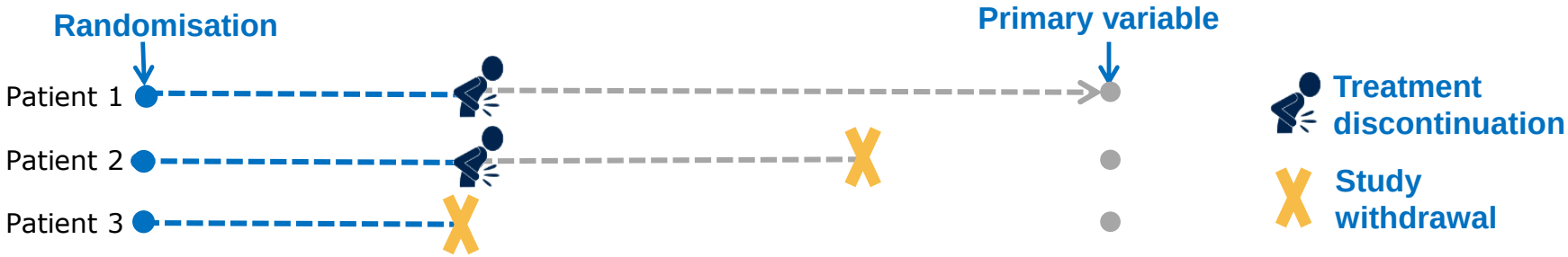
Intercurrent events versus missing data

Based on the ICH E9 (R1):

- Intercurrent events (ICE): “Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.”
- Missing data: “Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.”

Intercurrent events versus missing data



- **Assumption:** Treatment discontinuation not captured in other estimand attributes
- **Treatment policy strategy**:
  - Treatment discontinuation is an intercurrent event
  - Patient 1 has no missing data
  - Patient 2 and Patient 3 have missing data → missing data problem
- **Hypothetical strategy** ('had patients not discontinued treatment'):
  - Treatment discontinuation is an intercurrent event
  - Patient 1/2 have no missing data - even if the data was collected it wouldn't be meaningful for the estimand of interest → strictly speaking no missing data problem, but need to predict the hypothetical outcome and often will make use of missing data terminology and methods
  - Patient 3 has missing data

Missing data and predictions due to COVID-19 pandemic

Missing Data (MD)

- Can introduce selection bias
- MD assumptions need to be aligned with the estimand of interest
- For MD not associated with an ICE, an ignorable missingness assumption appears plausible
- From where/whom do we borrow information to 'impute' the MD?
- Do we have sufficent data/info to borrow from?
- Need to adequately account for the added uncertainty due to MD
- Sensitivity analyses to assess robustness of conclusions to plausible alternative assumptions

Predictions for hypothetical strategies

- Assumptions for the predictions need to be aligned with the hypothetical strategy of interest
- From where/whom do we borrow information to 'predict' the hypothetical measurements of interest?
- Do I have sufficient data/info to borrow from?
- Need to adequately account for prediction uncertainty
- Sensitivity analyses to assess robustness of conclusions to plausible alternative assumptions

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Estimand framework to the rescue?

YES...

- Helps to structure the problem and to assess the impact of COVID-19 complications on trial integrity
- Helps to distinguish between intercurrent events and missing data

Estimand framework to the rescue?

BUT...

- Alignment is needed on estimand choice in respect of unforeseen ICE
  - Is a treatment policy approach suitable?
  - If a hypothetical strategy is preferred, then which one?
  - When is a composite strategy advisable? Outcome trials?
  - In a recent FDA guidance, the removal of affected sites and patients is discussed as option → Which estimand ('WHAT') is implied by this approach ('HOW')?
  - Do considerations for efficacy and safety assessments differ?
- Robust estimation may be challenging if a) many unforeseen ICE occur and b) a large proportion of missing data is observed
  - For a) this is particularly true when estimand strategies other than treatment policy and composite are of interest
- Require rich information on unforeseen ICE (e.g. nature of event, duration, ...)

Thank you

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