Hypothetical strategy for a case study affected by COVID-19 pandemic

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Force majeure trial disruption

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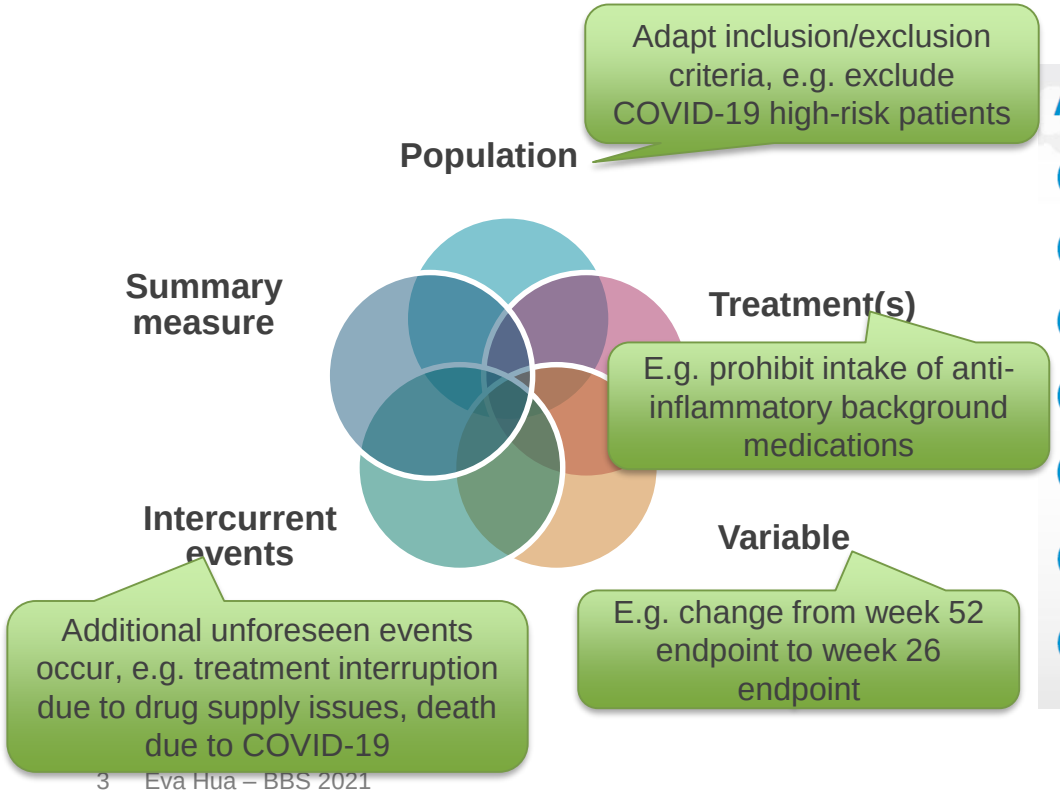
Estimand attributes are potentially impacted by COVID-19



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

8

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Case study – study design

- Two identical pivotal RCTs

- Multiple hypotheses tested in each dose level, e.g. «H1hp»
- Sufficiently powered for primary endpoint vs. active control, and vs. placebo

1: primary, **2-5**: secondary
h: high dose arm, **l**: low dose arm
p: vs. placebo, **c**: vs. active control

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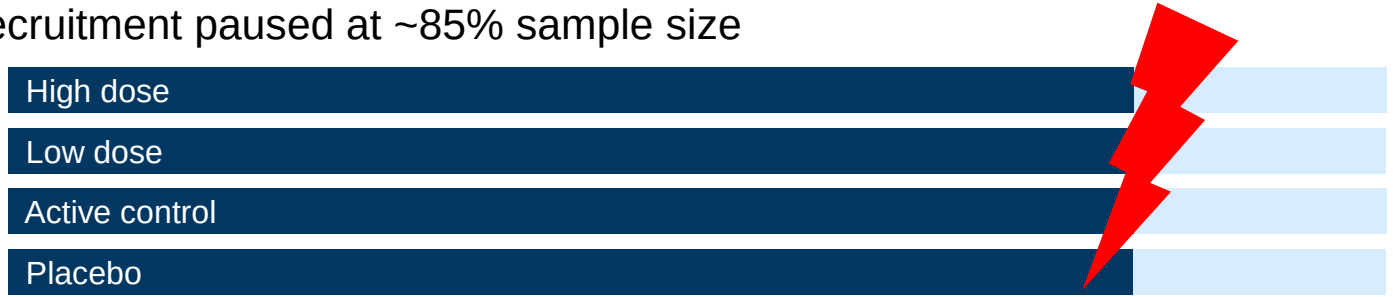
Hua et al. (2021)

Case study – COVID-19 pandemic impact

- Some impact of the COVID-19 pandemic
  - Recruitment paused at ~85% sample size



  - patients infected with COVID-19, treatment interruptions, missed visits
- Impact on treatment effect of interest is uncertain and unforeseen
- Enrollment *might* be able to re-start at a later time

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Case study - Original planned primary estimand in the protocol

- **Foreseen intercurrent events (ICE)*:** intake of rescue medication; discontinuation of study treatment due to adverse events or lack of efficacy or any other reasons
- **Original plan:** treatment policy strategy for all ICE
- Should we adapt the estimand given the unforeseen intercurrent events, e.g. treatment discontinuation due to COVID-19 pandemic?

*simplified for this presentation

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Case study - Complications due to the pandemic

Complications due to administrative / operational challenges

- treatment discontinuation due to drug supply issues or 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;
- inability of COVID-19 infected subjects to attend scheduled visits;
- health issues due to/exacerbated by health system overload or government restrictions

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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 is 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

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Case study - New primary estimand under COVID-19 pandemic

- Primary estimand strategy change: to provide an estimated treatment effect in a world where the COVID-19 pandemic does not exist.
  - Add new intercurrent event due to COVID-19 happen. It will be handled through the hypothetical estimand
    - treatment discontinuation
    - reduced treatment adherence (missed doses, missed visits)
    - and/or rescue medication/prohibited medication taken due to COVID-19, occurring prior to primary endpoint time point
  - Other options of having this potential COVID-19 impact through sensitivity analysis or supplementary estimand could be considered, if the impact is not a concern to bias our results.

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Case study - Health authority feedbacks

CHMP feedback on the proposed new intercurrent events:

- “In essence, if the intercurrent event observed during the COVID-19 affected period is not considered treatment related (i.e. lack of efficacy or safety issues) then the hypothetical strategy is considered acceptable [...]”.

- “A discussion is lacking on how an intercurrent event would be attributed to COVID19 and to COVID19 only, and associated data collection requirements to facilitate this.”

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Case study - Updated new primary estimand under COVID-19 pandemic

- Primary estimand strategy change: to provide an estimated treatment effect in a world where the pandemic-related operational challenges do not occur.
  - Add new intercurrent event due to COVID-19 operational complication happen. It will be handled through the hypothetical estimand
    - treatment discontinuation purely due to COVID-19 operational complications
    - Reduced treatment adherence (missed doses, missed visits) due to COVID-19 operational complications
    - ~~And/or rescue medication/prohibited medication taken due to COVID-19, occurring prior to primary endpoint time point~~
  - Other options of having this potential COVID-19 impact through sensitivity analysis or supplementary estimand could be considered, if the impact is not a concern to bias our results.

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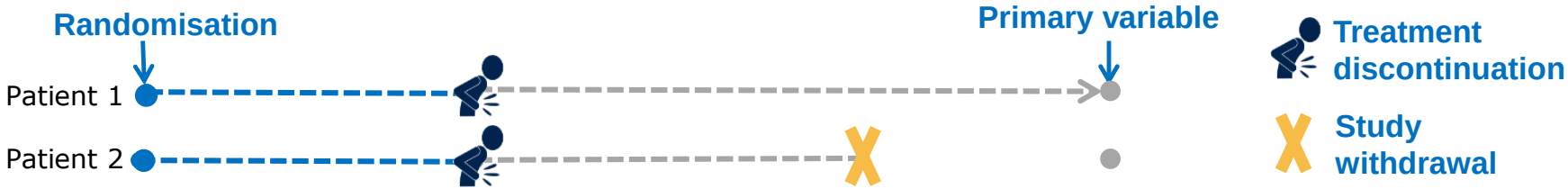
Case study - Estimation for hypothetical estimands

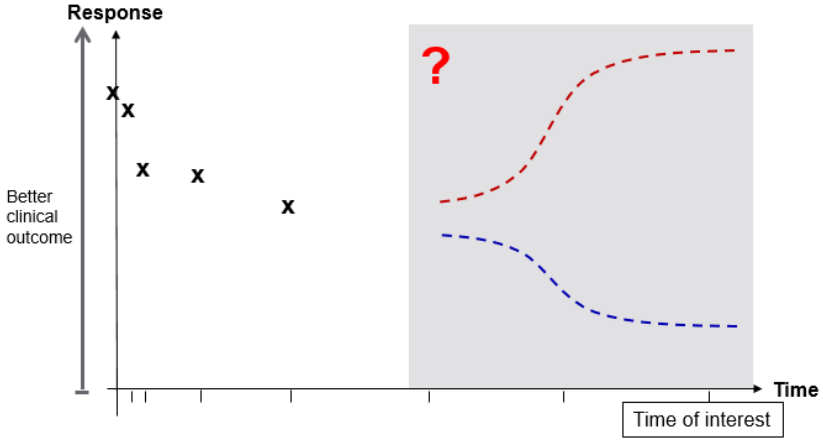
- Requires prediction of hypothetical trajectories
- Example for illustration:



  - Treatment discontinuation is an intercurrent event for which a hypothetical strategy is used
  - Data collected after trt discontinuation for Patient 1 and Patient 2 is (usually) irrelevant for estimating a hypothetical estimand
  - This does not constitute a missing data problem, rather we need to predict the hypothetical trajectories

Case study - Prediction of hypothetical trajectories

- For the COVID-19 related intercurrent events due to operational complications, data after the intercurrent events will be removed and replaced by data predicted using the missing at random (MAR) assumption for both arms.
- Data after the non-COVID-19 related intercurrent events would be included in the modelling for multiple imputation which is based on sufficient retrieve-drop-out data in the same treatment arm or borrow the information from placebo arm under the missing not at random (MNAR) assumptions.
- To adequately account for prediction uncertainty, a sensitivity analysis will be performed.



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Case study – Discussion

- The study team discussed complications due to the COVID-19 pandemic following the estimand thinking process.
- The hypothetical strategy chosen for the pandemic-related intercurrent events required a re-consideration of the target sample size.
  - COVID-19 impact on the study data integrity needs to be closely monitored
  - Additional COVID-19 related sensitivity and supportive analyses need to be considered for the unforeen risks of prediction based on hypothetical strategy
- Other than the COVID-19 related intercurrent events added for the primary estimands, additional risk mitigation strategies also should be evaluated by the study team

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