Trial integrity in view of the COVID-19 pandemic

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BBS Seminar - Impact of COVID-19 on clinical trials

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Outline

1. Trial integrity
2. Complications arising from COVID-19 pandemic
3. Intercurrent events versus missing data
4. Estimand considerations
5. ‘Missing data’ considerations
6. Other statistical considerations
7. Conclusions

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;
- inability of COVID-19 infected subjects to attend scheduled visits;
- health issues induced or exacerbated by the government restrictions or the health system overload

Characteristics of these complications

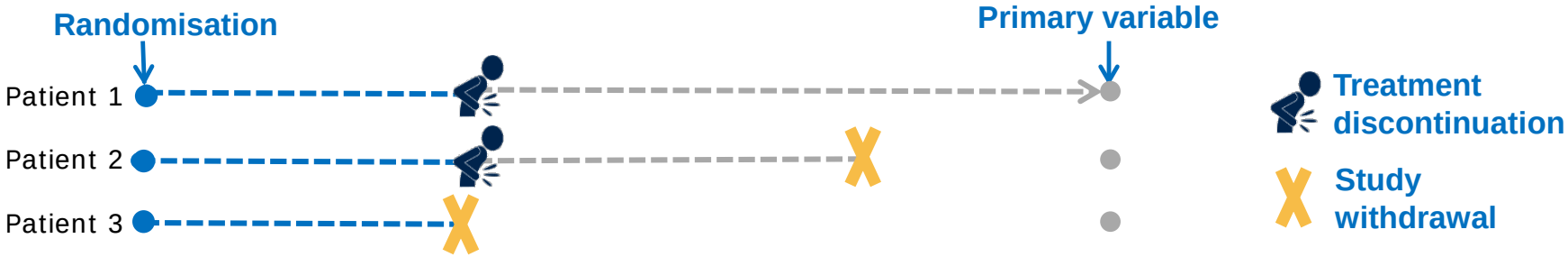
- Unforeseen at design stage
- May be a direct consequence of measures taken because of the pandemic
- Often expected to apply similarly to different treatment arms
  - exceptions exist, e.g., open label trials or trials which contain immunosuppressive drugs
- Extent of the complications will likely 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 of these events affect either the interpretation or the existence of the measurements associated with the clinical question of interest (intercurrent events)
- Some complicating events prevent relevant data being collected and result in a missing data problem

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

Estimand considerations

- It seems important to distinguish between COVID-19 pandemic related and unrelated ICE
  - E.g., ‘treatment discontinuation due to drug supply issues caused by the pandemic’ versus ‘treatment discontinuation due to lack of efficacy’
- For ICE foreseen at the planning stage there appears to be no need for action
- For unforeseen ICE, need to re-phrase the planned estimand to account for them
  - No mention/adaptation implicitly suggests a treatment policy approach
  - Interplay of foreseen and unforeseen ICE is important
  - In which cases is a hypothetical strategy more relevant? Which hypothetical strategy?
  - Do we need to distinguish between ICE related to operational challenges versus ICE related to health status of the patient?
    - A hypothetical question seems plausible for ICE related to operational challenges
    - Less clear for ICE related to the health status, e.g. death due to COVID-19 in COPD trial

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

Additional statistical considerations

- Specific challenges may result in the setting of open-label and single arm trials
  - differential rates of study and treatment discontinuations might be observed
  - may need to re-assess the level of comparability and relevance of historical data, to the data collected in the trial
- Data quality concerns should be addressed through sensitivity analyses
- Consistency of treatment effects by region or of the population before, during and after the COVID-19 pandemic may need to be investigated
  - What is meant by consistency?
  - How to define before/during and after COVID-19 pandemic?
- Power implications are to be expected
  - For certain decisions, it may be helpful to approximate the current operating characteristics based on data existing so far

More scientific discussions are needed

- What type of consistency analyses are useful and what are their operating characteristics?
- Can modifications to success criteria be considered and, if so, what methods and justifications should be developed?
- Are there acceptable approaches to compensate for lost information (beyond increasing sample size, extending follow-up times etc.)?
- What are relevant safety estimands and should these be aligned to the efficacy estimands?
- How can we derive consistent benefit-risk conclusions?
- What is the role of DMCs for trial integrity assessments?

Conclusions

- COVID-19 pandemic has an impact on clinical trial integrity and interpretability
- Various complications arise, some of which are more of operational nature (conceptually less problematic) while others are related to the health status of patients (potentially more problematic)
- Complications can result in intercurrent events, missing data and data of poor quality
  - Need to rephrase estimand in view of unforeseen intercurrent events
  - Need to decide on appropriate assumptions/methods for imputations/predictions
  - Need to adapt analysis plans
- More broadly, the pandemic has an impact on power, consistency of treatment effects,...
- Crucial to collect data to allow distinction of foreseen/unforeseen ICE and their duration
- Various questions remain unanswered and call for discussions and alignment between industry, regulators and academia

Thank you

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