Trial integrity in view of the COVID-19 pandemic

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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.”
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 sufficient 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