STATISTICAL ISSUES AND RECOMMENDATIONS FOR CLINICAL TRIALS CONDUCTED DURING THE COVID-19 PANDEMIC

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Pfizer GLOBAL PRODUCT DEVELOPMENT

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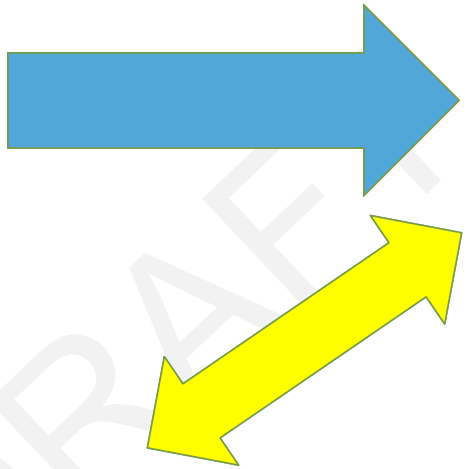
Outline

- COVID-19 affects on clinical trials
  - Assessing impact of COVID-19 on ongoing clinical trials
  - Define risk to study integrity, conduct, analysis and interpretation
- Statistical analysis modifications
  - Estimands
  - Missing data
  - Characterize the pandemic impact
- Conclusions

COVID-19 Disruptions to Clinical Trials

DISRUPTIONS

- Quarantines, travel limitations, site closures or reduced availability of site staff
- Interruptions to supply chain of experimental drug and/or other medications
- COVID-19 infection / treatment



IMPACTS

Missed or delayed visits, assessments

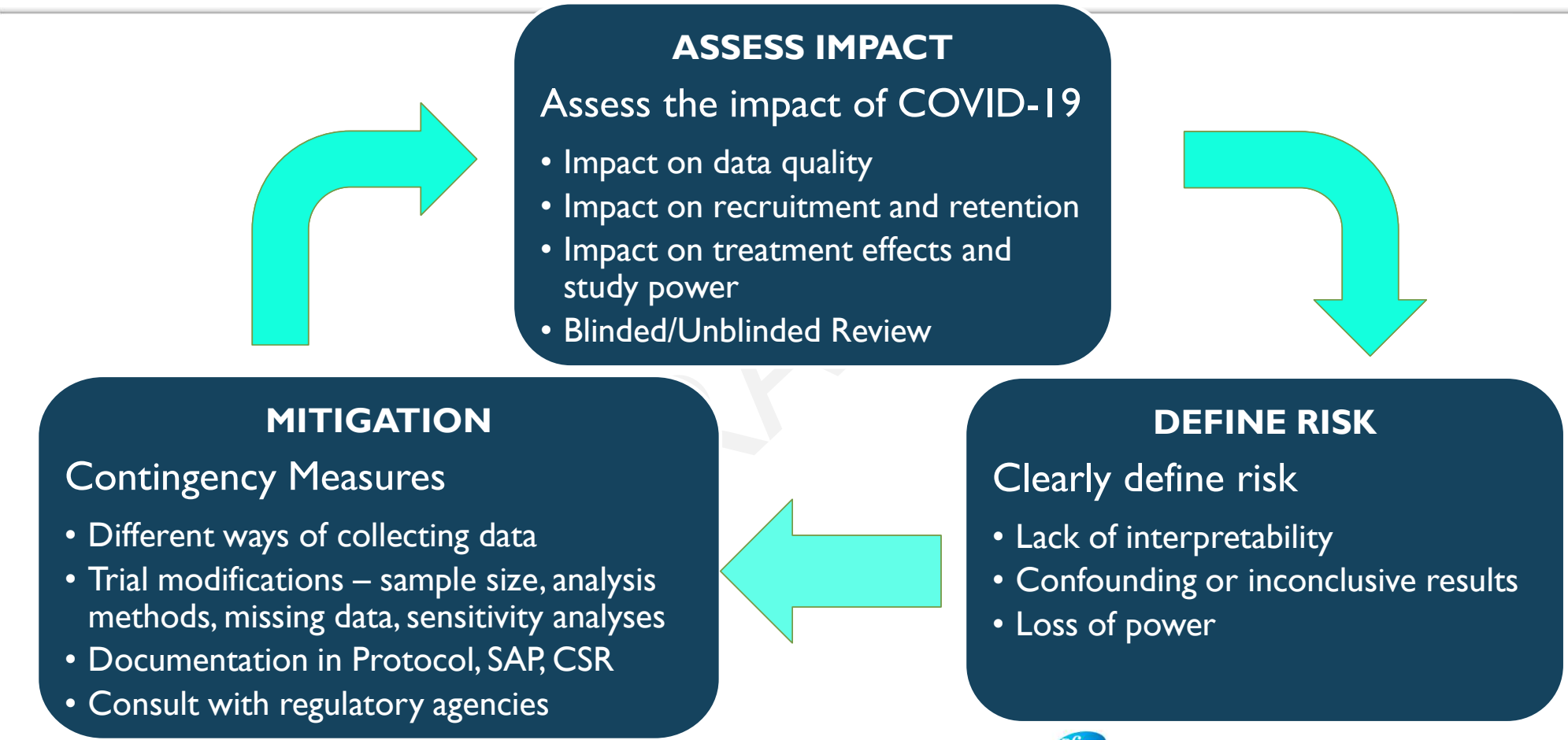
Treatment interrupted

Data missing, perturbed, interpretability affected

MITIGATIONS

- Decentralized visits, telemedicine
- Alternative assessment procedures
- Trial design modifications
- **Modified statistical analyses**

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

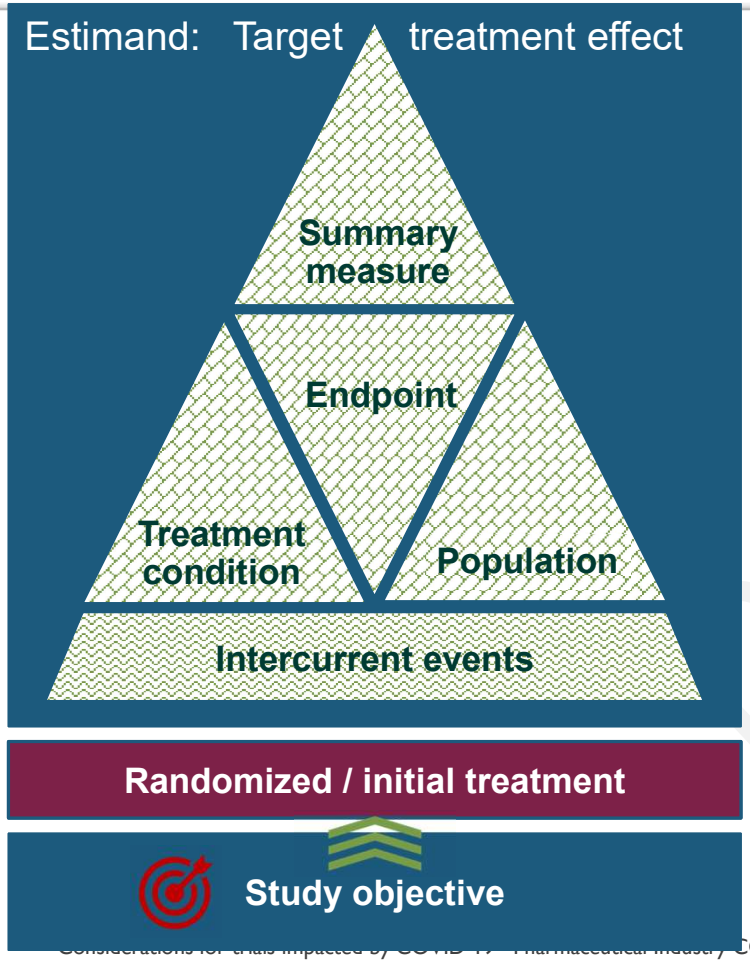


Implications to Study Population, Estimands, Planned Analyses

Prespecify pandemic-related updates in protocol/SAP, and document analyses in CSR

- Baseline characteristics by enrolment phase (pre-, post-pandemic onset)
- Study disposition e.g. patients/assessments impacted, treatment interruption/discontinuation, study withdrawal
- Summarize protocol deviations due to pandemic
- Efficacy
  - Estimand considerations (revised, new, unchanged)
    - Identify new pandemic-related intercurrent events and associated strategy
  - Address the extent of missing data caused by the pandemic
  - Revise planned analyses if needed
- Safety
  - Identify COVID-19 AE terms and concomitant medications
  - Discuss impact of pandemic-related missing data on safety interpretation

Estimand framework – unnecessary complication or 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

Does COVID-19 change my research question?

The current COVID-19 outbreak may lead to a need to reaffirm the original research question or consider new exploratory research question:

1. How would Drug A compare to Drug B **in the absence of COVID-19 pandemic**?
2. In specific situations: how does Drug A compare to Drug B **in the presence of possible individual COVID-19 infections**?

Assess the impact on each of the five estimand attributes per ICH E9(R1):

- Treatment condition of interest
- Population of patients targeted by the clinical question
- Variable (endpoint) to be obtained for each patient
- Handling of other intercurrent events
- Population-level summary providing a basis for comparison between treatment conditions

Key Pandemic-Related Intercurrent Events

Subject's Study Treatment Condition	Study Treatment Accessibility	Subject's COVID-19 Infection Condition	Subject's COVID-19 Concomitant Treatment(s)
• Discontinued and no new treatment started • Discontinued and switched to alternative/SoC • Interrupted or compliance significantly reduced • Interrupted or compliance significantly reduced with changes in the concomitant study disease therapy, e.g., start of rescue medications	• Drug supply interruption • Site unavailable for administration/dispensing • Study treatment available but subject is unable/unwilling to get study treatment due to personal pandemic-related reasons	• Known COVID-19 infection • Positive for COVID-19 • Deceased due to COVID-19	• Subjects treated for COVID-19 (pharmacologically, oxygen, etc.) • Hospitalized, not in ICU • ICU

Addressing intercurrent events – 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 COVID-19 related intercurrent events.

Strategies for pandemic-related ICEs

- **Treatment policy** – if already used for non-pandemic ICE and low number of pandemic-related ICE
- **Composite** – unlikely to be applicable; perhaps in respiratory trials. But if already used for non-pandemic ICE and low number of pandemic-related ICE, may be fine.
- **Principal stratification** – unlikely to be applicable
- **Hypothetical** – natural choice for pandemic-related ICEs; impute hypothetical outcome in absence of COVID-19

Pandemic-related factors and missingness mechanism

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

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

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
- Negative binomial model
- 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

Additional Analyses in Context of COVID-19

- Additional Sub-group Analyses
  - Clinical Trial periods with respect to COVID-19 outbreak onset and duration
  - Geographical regions
  - Data sources
- Additional Analyses to Assess the Impact of Missing Data
  - Sensitivity analyses to assess departure from MAR assumption
  - Borrowing historical data/RWD/epidemiological
- Additional Safety Analyses
  - Summary of COVID-19 infections or other AE of interest due to COVID-19
  - Summary excluding a) data after COVID-19 infection, b) events related to COVID-19 infection

Conclusions

- WE CAN DO THIS
- Continual cycle of assess / define / mitigate
- Estimand framework valuable for characterizing impacts on data
  - Even if study not originally defined in those terms
  - Pandemic-related intercurrent events
- Accomodating missing and perturbed data in analyses
  - Pandemic missing data often are MCAR or MAR
  - Rich array of methodology available including multiple imputation
- Characterize overall pandemic impact on trial

Select References

Statistics in Biopharmaceutical Research, special issue on COVID-19

- **"Statistical Issues and Mitigations for Pharmaceutical Clinical Trials Conducted During the COVID-19 Pandemic. (with discussion)" Pharmaceutical Industry COVID-19 Biostatistics Working Group**
- "Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework." Oncology Estimands Working Group
- "Challenges in Assessing the Impact of the COVID-19 Pandemic on the Integrity and Interpretability of Clinical Trials." Akacha et al

FDA Guidances

- Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry
- Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

EMA Guidances

- GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC
- Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials