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Safety Assessment for Studies and Submissions Impacted by COVID-19

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Agenda

- Introduction
- Assessing COVID-19 Impact
- Comparing Adverse Events Among Treatments
- Summarizing Adverse Event Data Without a Control
- Analyses of Laboratory Data
- Safety Topics of Interest
- Concluding Remarks

Introduction

- PHUSE is an independent, not-for-profit organization run by volunteers
  - Global platform for discussion
  - Data managers, biostatisticians, statistical programmers, and IT professionals
- In 2012, PHUSE and the FDA created a collaboration
  - Recommended safety analyses
  - Robust, public peer review process

PHUSE Safety Analysis White Papers and Workshop

Go to phuse.eu Click on “Working Groups,” then click on “Deliverables”				
2013 Labs: Central Tendency	2015 Labs: Outliers/ Shifts	2017 Adverse Events	2018 Medications	2019 Safety Workshop

Introduction (continued)

- Impact of COVID-19 on scientific evaluation of safety data
  - Guidance on how to simply and properly reframe the analyses
- Safety analyses have two main purposes
  - To help determine which AEs are causally related to the drug (ADRs)
  - To quantify risk of ADRs in labeling and other risk communications
- Need medical assessment of the analyses
  - Medication class effects, biological plausibility, and other clinical considerations

Assessing COVID-19 Impact

- To assess the safety of study participants
  - Variables that apply differentially across treatment groups
  - Patient characteristics (such as gender, age, race)
  - Aspects of study conduct (such as discontinuations, missed visits, protocol deviations, and number of missed doses)
- Potential impact of any differences should be considered

Comparing Adverse Events Among Treatments

- To determine if there are any important imbalances
  - Among treatment groups disfavoring study drug
  - Suggestive of a causal relationship
- Unless COVID-19 impact is considerably different across treatments
  - Analytical plans can generally remain unchanged
  - Estimates may not be useful for quantification of risk

Summarizing Adverse Events Without a Control

- Potential for overestimation/underestimation from COVID-19 impact
  - Especially when interpreting uncontrolled data against other sources
- When comparing an EAIR with another source
  - Summarizing up to COVID-19 impact or by COVID-19 subgroups
  - Based on some objective measure of COVID-19 impact
  - For example, patients who had study visits impacted by COVID-19 versus patients who did not have any study visits impacted by COVID-19

Analyses of Laboratory Data

- When a central lab is normally used for a study
  - But local labs are subsequently used due to COVID-19
- If local lab measurements were not brought into the study database
  - Analyses would be conducted with less complete data
- Combining local and central labs could provide more complete data
  - Additional variability and uncertainty can be added into the data
- Need clarity on if and when local and central lab measurements are combined

Comparing Lab Shifts

- Comparing percentages of patients shifting to low/high
  - To assess imbalance among treatment arms
- Unless impact from COVID-19 is different across treatment groups
  - Analytical plans can mostly remain unchanged
- Combining measurements from local and central labs
  - Limits from associated lab should be used

Simple Summary Statistics by Visit

- Summarizing changes over time by treatment
  - For example, box plots by visit with means or mean changes
- If there are a substantial number of missed visits
  - Mixed model for repeated measures (MMRM) may be more appropriate than simple means
- Need to decide which laboratory measurements to combine
  - Report data as percent above/below normal limits
  - A normalization method could be used

Hepatotoxicity

- Expectation to assess potential for drug-induced liver injury
  - Limits from local lab should be used
- If local labs are not brought into the study database
  - Potential for missing Hy's law cases

Safety Topics of Interest

- Special consideration is needed for safety topics of interest
  - Additional or alternative methods might be warranted
  - Summaries up to COVID-19 impact or by COVID-19 subgroups
- In choosing among alternative methods
  - Connect method with eventual interpretation
  - Understand the pros and cons of various choices

Concluding Remarks

- Safety assessment for studies impacted by COVID-19
  - Remain focused on establishing benefit/risk of the product
- If impact is considerably different among treatment groups
  - Different or additional analyses should be considered
- If impact is not different
  - Analyses should generally be carried out as planned
  - Special consideration is needed for safety topics of interest
  - Different methods of risk quantification may be needed for ADRs
  - Update analysis plans if combining local and central labs

Main Message

For clinical study reports and submissions,

stay focused on establishing the benefit/risk

of the investigational product

Avoid Unnecessary Complications

Clinical Trial Drug Safety Assessment for Studies and Submissions Impacted by COVID-19

Special Issue for *Statistics in Biopharmaceutical Research*

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Questions?

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Quantification of Risk and Product Labeling

- When communicating about ADRs in labeling
  - Cautionary language on limitations of comparing with other labels
- When there is a large impact from COVID-19
  - Cautionary language might need to be expanded
  - Depending on how it may have been impacted by COVID-19
  - Need to be attentive to the summary metrics used to quantify risks