Estimand Framework in Addressing COVID-19 Impact on the Ongoing Clinical Trials

Vlad Dragalin, PhD

Vice President, Head of Quantitative Sciences Consulting
Janssen Pharmaceuticals

Drouville, *In the fish tank*

Drouville is a patient, graphic designer and artist from Argentina who has survived multiple myeloma and a relapse.

PS6c – Estimands: Application of the Framework in Answering the Question of Interest in Drug Development | BIOP 2020

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OUTLINE

1. Recent Guidances and Publications
2. Potential Impact on Estimand Attributes
3. **Potential Impact on Estimation**

Regulatory Agencies Guidances

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Version 3

28/04/2020

Contains Nonbinding Recommendations

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on July 2, 2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 26 June 2020
2 EMA/158330/2020 Rev. 1
3 Committee for Human Medicinal Products (CHMP)

4 Points to consider on implications of Coronavirus disease
5 (COVID-19) on methodological aspects of ongoing clinical
6 trials

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Recent Publications

Article

5785
Views

Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic ›

R. Daniel Meyer, Bohdana Ratitch, Marcel Wolbers, Olga Marchenko, Hui Quan, Daniel Li, Christine Fletcher, Xin Li, David Wright, Yue Shentu, Stefan Englert, Wei Shen, Jyotirmoy Dey, Thomas Liu, Ming Zhou, Norman Bohidar, Peng-Liang Zhao & Michael Hale

Latest Articles
Published online: 6 Jul 2020

Article

1542
Views

Comment on "Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic" ›

Sylva H. Collins & Mark S. Levenson

Latest Articles
Published online: 6 Jul 2020

Article

794
Views

Under a Black Cloud Glimpsing a Silver Lining: Comment on Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic ›

Rob Hemmings

Latest Articles
Published online: 14 Jul 2020

Statistics in Biopharmaceutical Research, 2020

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Recent Publications

Article

1199 Views

Challenges in Assessing the Impact of the COVID-19 Pandemic on the Integrity and Interpretability of Clinical Trials ›

Mouna Akacha, Janice Branson, Frank Bretz, Bharani Dharan, Paul Gallo, Insa Gathmann, Robert Hemmings, Julie Jones, Dong Xi & Emmanuel Zuber

Latest Articles
Published online: 17 Aug 2020

Article

1344 Views

Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework ›

Evgeny Degtyarev , Kaspar Rufibach , Yue Shentu , Godwin Yung , Michelle Casey , Stefan Englert , Feng Liu , Yi Liu , Oliver Sailer , Jonathan Siegel , Steven Sun , Rui Tang , Jiangxiu Zhou & on behalf of the Industry Working Group on Estimands in Oncology

Latest Articles
Published online: 14 Jul 2020

Article

1644 Views

Efficient Adaptive Designs for Clinical Trials of Interventions for COVID-19 ›

Nigel Stallard, Lisa Hampson, Norbert Benda, Werner Brannath, Thomas Burnett, Tim Friede, Peter K. Kimani, Franz Koenig, Johannes Krisam, Pavel Mozgunov, Martin Posch, James Wason, Gernot Wassmer, John Whitehead, S. Faye Williamson, Sarah Zohar & Thomas Jaki

Latest Articles
Published online: 29 Jul 2020

Statistics in Biopharmaceutical Research, 2020

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Impact on the Treatment Effect Evaluation

- The ongoing trials during the COVID-19 pandemic can be impacted in various ways by this outbreak.
- The impact of COVID-19 needs to be assessed with regards to all aspects related to statistical activities.
- This includes what data are being collected and how they are being collected, alongside subsequent statistical analysis and interpretation.
- Statistical analyses should take into account changes from the protocol and statistical analysis plan.
- In order to be able to do this it is vital that such information is collected in a formal, documented manner, so that it is subsequently available for statistical analyses and the interpretation of results.

Impact on the Treatment Effect Evaluation

- Each trial needs to be examined to determine if its objectives and scientific questions of interest can still be evaluated in the presence of this pandemic.
- If not, the trial might need to be modified and consequently the estimands would need to be updated and appropriately communicated to health authorities.
- Additional/supplementary estimands/analyses could also be considered as they can lead to different perspectives on treatment effect estimates.
- The COVID-19 impact on an ongoing trial can be manifested by:
  - Participants being infected with COVID-19 (confirmed by a test or not)
  - Trial conduct being affected by the lockdown triggered by the pandemic, some of the trial conduct changes having also a direct impact on participants (e.g. missed doses or treatment discontinuation).

Potential Impact on Estimand Attributes

The framework of the ICH E9(R1) Addendum needs to be followed.

A definition of the treatment effect (i.e. an estimand) could also be affected, together with any corresponding analysis method (estimator).

Treatment

- In most cases the treatments will remain the same, but treatment regimen may be affected (delayed, interrupted, or stopped due to COVID-19 infection, different delivery)
- If appropriate, evaluate if the control definition needs to be expanded (e.g. with use of Bayesian control borrowing from historical data, if this can be justified and useful).

Population

- As the estimand attribute, the target population would remain unchanged. However, the trial participants enrolled before, during and after the start of the pandemic might represent differently the target population. This needs to be addressed in the analysis.

Potential Impact on Estimand Attributes

Variable / Endpoint

- If the trial contains participants infected with COVID-19, evaluate if the pre-planned endpoint needs to be adjusted, e.g. counting the COVID-19 infection as a negative outcome, so using the composite strategy for this type of intercurrent event.
- Otherwise, evaluate the pre-planned endpoint:
  - Can it still be collected during the pandemic?
  - Define when an endpoint is considered missing or affected by the pandemic and evaluate the potential impact of its missing/affected values on power and other trial characteristics (e.g. by simulation).
- If needed, evaluate changes in the endpoint (i.e. different timing, type of collection) or alternative endpoints relevant to same indication.

Potential Impact on Estimand Attributes

Summary Measure

- Evaluate if a different summary measure might better reflect the effect of the treatment comparison of interest in the presence of these new ICEs and potentially larger amount of missing values,
  - e.g. replacing mean by median
  - or replacing hazard ratio by percentage of subjects with an event by a certain time point (to avoid the proportional hazard assumption).

Potential Impact on Estimand Attributes

Intercurrent Events (ICEs) and Corresponding Strategies

- Determine what types of events related to the COVID-19 pandemic are considered ICEs (to be accounted for in the estimand definition) or protocol deviations (potentially to be accounted for in analysis).
- Examples of new potential ICEs (not planned in the original protocol), which can affect the existence or the interpretation of the endpoint:
  - death or another major health outcome due to infection with COVID-19
  - treatment discontinuation due to infection with COVID-19
  - initiation or intermittent use of concomitant medication due to infection with COVID-19 (which could be protocol prohibited or not planned in the original protocol) that could impact the endpoint
  - psychosocial impact of the start of the pandemic
  - treatment discontinuation due to trial conduct affected by COVID-19
  - severe treatment non-compliance due to trial conduct affected by COVID-19.

Potential Impact on Estimand Attributes

Intercurrent Events (ICEs) and Corresponding Strategies

- Examples of protocol deviations related to COVID-19, not considered ICEs:
  - out of window or missed measurements due to the pandemic
  - minor treatment non-compliance due to COVID-19
  - initiation or intermittent use of protocol prohibited concomitant medication due to infection with COVID-19 that does not impact the endpoint.
- Some protocol deviations related to COVID-19 might lead to missing or uninterpretable observations.
- They would need to be addressed in the trial estimators and their assumptions.
- For some of the protocol deviations, the decision might be to not use the observations collected after these deviations; these observations will then be considered missing in analysis.
- Assumptions will need to be specified for them, to be aligned with the proposed analyses.

Strategies for the new ICEs

- Trial estimands need to be updated in protocols and/or SAPs with the COVID-19 related new ICEs and the corresponding strategies to address them.
- The original estimands will still be included and there will be clarity on what updates are included as a result of the pandemic impact.
- Examples of strategies to be used for the new ICEs:
  - Hypothetical: e.g. as if COVID-19 pandemic would not have occurred; it may be appropriate for ICEs that affect trial conduct;
  - Composite (see endpoint component): e.g. if participants are considered to have a negative outcome if experiencing a major health outcome due to infection with COVID-19;
  - Principal Stratum: e.g. considering the stratum of participants who were not affected by the pandemic or who adhered to treatment for the trial duration;
  - Treatment Policy: e.g. when the impact of the ICE on the treatment effect evaluation is considered minimal.

Potential Impact on Statistical Analysis

FDA: Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (e.g., for protocol-specified procedures). It will be important to capture specific information in the case report form that explains the reasons for the missing data, including the relationship to COVID-19 for missing protocol-specified visits/procedures. This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.

- Develop procedures to capture additional COVID-19 information to identify the new intercurrent events related to COVID-19, the new protocol deviations and help with the characterization of the missing information.
- If appropriate, assess alternative ways of obtaining elements of missing data e.g., surveys, 'virtual' visits, e-health data.
- Provide summaries of each COVID-19 related intercurrent event.
- Provide summaries of the COVID-19 related protocol deviations and affected disposition.

Handling Missing Information

- Propose estimators/analyses that are aligned with any estimands modified because of the COVID-19 pandemic.
- Provide clarity on what information is considered missing under each estimator and what assumptions are used.
- Characterize the type and amount of missing data for each estimator.
- Most data that are missing due to trial conduct being affected by the pandemic may be argued to be MCAR or MAR.
- Perform a broad range of sensitivity analyses (e.g. tipping point) around resulting missing observations due to participants being infected with COVID-19.
- Perform supplementary analyses, e.g. using different strategies for the ICEs related to COVID-19.
- Explore supplementary analyses using historical clinical trial data or real-world data to support assessment of the impact of missing data elements.
- Consider longitudinal modeling as a useful tool to use the totality of data, handle missing values, and potentially adjust for the onset of the COVID-19 pandemic.

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Conclusions

- The ICH E9(R1) Addendum provides a useful framework for assessing the impact of the COVID-19 pandemic on the primary study objectives in a systematic and structured manner.

- COVID-19 related intercurrent events should be clearly defined, perhaps through an amendment to the protocol and/or SAP, and the appropriate strategies should be considered to address their impact on the main estimand.

- Additional supportive and sensitivity analyses may be required to evaluate the COVID-19 impact on the treatment effect evaluation.

THANK YOU FOR YOUR ATTENTION

Vlad Dragalin, vdragali@its.jnj.com

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