The Impact of COVID-19 on Clinical Trials in Neuroscience:
Comments and Proposals of the European Working Group on Estimands in Neuroscience

Sponsored by EFSPI and PSI

Andrew Hartley, PhD
Statistical Science Director, PPD

HELPING DELIVER LIFE CHANGING THERAPIES

PPD®

Overview

+ General thoughts
+ Current observations
+ Potential impacts of COVID-19
+ Immediate and later mitigation steps
+ Some recommendations
+ Summary

+ Slide set is a living document, supporting ongoing discussions on ensuring
  + Subject safety
  + Trial validity and integrity

  during the pandemic

General Thoughts

- Pandemic
  - Currently impacts practically all clinical trials
  - Can impact clinical trial conduct and outcomes directly and indirectly
    - Direct impacts via additional AEs and deaths
    - Indirect impacts via
      - missed doses
      - missed visits and assessments
      - standards of care
      - levels of monitoring
      - PRO endpoints (due to additional emotional burdens)

General Thoughts (cont.)

- Most important: Document impacts of pandemic
- Make documentation
  - Easily accessible
  - Simple, but interpretable to determine categories of impacts
  - Transparent in reflecting
    - The how and the what
    - Reason
    - General vs. special impact
- Decide roles of DMCs in
  - Determining general vs. special impacts
  - Recommending mitigation measures
- Determine how to support DMCs in fulfilling those roles
- Subject safety comes first, even if prioritizing it causes protocol violations

General Thoughts (cont.)

- More severe pandemic impacts expected on studies in / with
  - Patients with many risk factors (e.g., elderly) for COVID-19
  - Chronic conditions
  - Neurodevelopmental indications
  - PROs as key endpoints
  - Complex routes of treatment administration
  - Treatment administration that depends on many site visits
- Less severe impacts expected on studies in / with
  - Emergency conditions
  - Life-threatening diseases
- Estimands helpful, especially in
  - Non-inferiority trials
  - Studies at sites occupied by pandemic

Current Observations

- Many NS indications are non-life threatening
  - Especially depression, Alzheimer's Disease or other diseases in elderly patients
  - So, many NS trials impacted more severely by pandemic
- Missing dosing, visits and assessments - frequent
  - Extents of missingness are still difficult to estimate
  - Teams focusing on immediate mitigation steps and documentation of missingness
- COVID-19-specific events (like AE or death) - not that frequent
- For multiregional trials: Regions will return to normal at different times. How to determine when they do?

Current Observations (cont.)

- Missed treatment can jeopardize objectives
  - Generally, difficult to mitigate
  - Can make outcomes non-interpretable
    - Estimators target different estimands
    - Estimators target unknown estimands
- Missed assessments and visits
  - Often, less critical
  - Often, can be mitigated by assessing subjects at follow-up visits

Potential Impacts of COVID-19 and Mitigation

- Indirect impacts - often difficult to handle
- Too frequent missed doses and/or assessments may degrade study integrity so much that results
  - Are non-interpretable
  - Are interpretable but irrelevant
  - Depend excessively on assumptions
- Mitigation steps are likely needed; differentiate between
  - Immediate steps = for early study stages, to minimize harm to studies
  - Later steps = for analysis and reporting stages, to account for COVID-19

Mitigation: Immediate Steps

- Documentation of
  - Doses / assessments missed due to pandemic
  - Adverse events / deaths due to COVID-19 infection
- Keep documentation simple: Was event due to pandemic?
  - Enables handling such events differently in the analysis
  - Linking categorization to the event could, though, be complex
  - Preferred method
    - Use protocol violation tools
    - Link violations to analysis datasets
  - That may not suffice, though, as
    - Sites may not follow the guidance exactly
    - Process is complex for sites
  - Classifying as due to pandemic vs. not would suffice in many cases, but not in presence of differential missingness

Mitigation: Immediate Steps - Protocol Amendment

- Change duration of follow-up
- Change visit windows
- Sample size increase
  - To maintain power
  - A replacement strategy for patients with too many missed events may be more meaningful
- Prolong follow-up
  - To capture missed assessments, supporting interpolation
  - For missed doses only

Mitigation: Immediate Steps (cont.)

- Adjust trial conduct - can add flexibility / “cushions,” to
  - Overcome increased variability and missing data
  - Improve trial robustness
- Combine adjustments. Example:
  - Sample size allowing patient replacement and
  - Prolong follow-up
- Collect data through virtual visits
- Discontinue enrollment in centers unable to
  - ensure subject safety
  - adherence to protocol

Mitigation: Later Steps

- Steps at analysis stage, including
  - How to handle doses missing due to pandemic
  - How to handle assessments missing due to pandemic
  - How to handle adverse events and deaths related to pandemic

  Other indirect impacts of pandemic may be
    - Indication-specific
    - More difficult to repair
- Use estimand framework
- Start with main study objective's assumptions about pandemic: Estimate treatment effects in
  - Presence of pandemic (Treatment policy estimand)?
  - Absence of pandemic (Hypothetical estimand)?

Mitigation: Later Steps in Analysis (cont.)

- Treatment policy strategy
  - Follow SAP ignoring pandemic-relatedness
  - Handle intercurrent events (ICEs) due to pandemic same as other ICEs
- Hypothetical strategy
  - Decide what "in the absence of the pandemic" means
  - Principle: Estimate the treatment effect as if the pandemic never happened.
  - Then specify further:
    - Meaning for doses missing due to pandemic?
    - Handling ICEs leading to missing assessments due to pandemic?
    - Handling pandemic-related adverse events or deaths?

Mitigation: Later Steps in Analysis Estimand Framework

- New pandemic-related intercurrent events (ICE)
  - Treatment interruption due to pandemic
  - Treatment withdrawal due to pandemic
  - Treatment withdrawal due to coronavirus infection or suspected infection
  - Death due to coronavirus infection or suspected infection
- Annotate missing assessments as missing due to pandemic vs. not
- These events may need further specification (patient choice, investigator choice or pandemic lockdown)

Some Initial Recommendations

- For pandemic-related ICEs
  - Treatment policy strategy - not usually of primary interest
  - Hypothetical strategy – more often appropriate
- Considerations for hypothetical strategy
  - Usually displays weaknesses in estimation
  - But if sufficiently unaffected data are available, estimators could still converge to meaningful estimands
  - Ideally, estimands should support the trial's original objectives
  - When can such hypothetical estimands no longer be estimated?
  - Estimation procedures for hypothetical estimands will likely be study- or at least indication-specific

Some Initial Recommendations – AEs/Deaths Due to Coronavirus Infection

- General procedures/standard outputs for the reporting of COVID-19 events may be useful
- Indication-specific methods needed
- Coronavirus dx tests
  - not so accurate, so
  - don’t differentiate between confirmed and suspected infections
- Summarize separately in the analysis
- In primary time-to-event analyses, censor at time an event occurs

Summary

- Pandemic affects studies differently, even in same clinical indication
- More strongly affected: studies in chronic diseases and the elderly, including many NS disorders
- Suggest to differentiate between immediate and later mitigation steps
- Consider amending protocol, to
  - Prolong follow-up or
  - Increase sample size
- Handle most intercurrent events related to pandemic using hypothetical strategy
- Consult with regulators to ensure estimands are acceptable
- Handle AEs and deaths related to pandemic separately from other such events