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

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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