Regulatory viewpoints from EMA and FDA on contemporary challenges and strategies for conducting and analyzing clinical trials in the COVID-19 era

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Panel

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Submit Questions for panel in Q&A feature

Disclaimer

Comments by panelists from FDA and EMA reflect the views of the panelists and should not be taken as formal guidance from the regulatory agencies.

Part I

COVID-related intercurrent events in the context of the ICHE9 estimand framework

Moderator: Valentina Mantua

Handling of COVID-related intercurrent events

- Is a hypothetical strategy acceptable for handling COVID-19 related intercurrent events under the estimand framework **for efficacy analysis**?

- Which strategy should be used to handle intercurrent events related to COVID-19 **in the safety analysis**?

- Could **discontinuations** or **missing values due to COVID-19** (site closures, travel restrictions, or patients' reluctance to attend clinic visits) be considered as "missing at random" using a hypothetical strategy as the primary estimand?

- How should intercurrent events related to COVID-19 be handled **in the pre-planned interim efficacy analysis**, e.g. timing, number of events, missing data, strategy for handling intercurrent events in the estimand framework?

A clinical perspective on COVID-related intercurrent events and effects on treatment effect

- COVID-19 will most likely affect the occurrences of intercurrent events; e.g., it could decrease the opportunities for patient's taking alternative treatment, dropping out of the study, or even discontinuing the assigned treatment in some scenarios. On the other hand, it could force more completers to become non-completers. In brief, COVID-19 events will change the estimand framework. Q: What are the kinds of intercurrent events that are likely to be affected by the COVID-19 events and consequently affect the assessment of treatment effect? This question is addressed to **clinicians**.

- Children with neurodevelopmental conditions such as autism rely on a steady flow of behavioral interventions and school based treatments such as ABA, Speech therapy as well as OT and PT. These behavioral interventions form the basis of their care in the absence of medicinal treatments for the core symptoms of the condition. During COVID for the most part these behavioral interventions have been suspended, curtailed or terminated. We know that this can result in the regression of positive gains experienced as a result of these interventions. How does the **autism researcher** account for this bias in drug trials?

Comparing pre-COVID, during-COVID and post-COVID datasets

- In a clinical trial with the likelihood of smaller effect sizes and altered outcomes, due to home confinement and/or changes in other interventions, or direct effects from COVID19, how does the Agency(s) look upon **comparisons between pre COVID and during COVID data in the same trial**?

- What are appropriate statistical methods for **combining data from trials that include both remote and in- person assessments**. Does this represent another factor in a factorial design?

- For data obtained remotely in lieu of clinic visits due to COVID-19, the analysis plan could include both with or without these data. However, are there any guidance on the criteria of judging whether the combined **full analysis is still the primary analysis**? Are there concerns on the reduced statistical power of the sub-analysis without these data or on the fact that such subset may no longer represent the full population or the randomization ?

Part II

Remote assessment of outcomes

Moderator: Richard Keefe

Comparing Remote versus Traditional In-person Assessment Methods

- As "lessons learned" emerge from remote data acquisition, what is the regulatory perspective on **novel outcome measures that have been specifically built for remote assessment versus those that have incorporated methods for applying existing scales using remote technology?**

- A related question: Are the EMA and FDA able to be involved in research that would test the question whether a novel measure specifically tailored for remote assessment outperforms a traditional outcome measure in terms of signal detection and drug-placebo differences?

- Few performance-based outcomes (PerfOs) have been validated for unsupervised administration. What is the agency's position on accepting data from remote unsupervised PerfOs during an ongoing clinical trial that transitions to remote/virtual data collection because of COVID-19? Will the reliability and validity data collected during the trial provide sufficient assurance that the remote administrations had similar psychometric characteristics to the traditional in-person assessments?

Addressing missing information from rating scales completed remotely

- In some trials, key rating scales such as the PANSS or MADRS cannot be completed in-person due to Covid-related restrictions. **What is the regulatory perspective on the assessments being completed remotely by telephone or video?** If telephone is acceptable, some observational items will be missing.

- Many clinician-administered rating scales require observation of the research participant by an observer, such as a caregiver or study partner. Due to Covid, these observers may be less available to clinical assessors and/or the frequency of their contact with the research participant may be significantly reduced. **Is it permissible to systematically omit certain items from a validated rating scale? How would missing data be managed under these circumstances? Also, would it be possible to combine data collected with different methods when a change occurs during a trial?**

Interpretation of data collected during Covid-19

- The effects of a change in modality from in-person to remote assessment and an increase in Covid-related psychosocial stressors could increase or decrease variability in outcome measures. How will such results be interpreted? Might they indicate a loss of instrument sensitivity to change?

Part III

Changes in safety assessment

Other statistical and regulatory issues related to the COVID-19 pandemic

Moderator: Michael Davis

COVID-19-related changes to safety monitoring plans

- What are the agencies' positions on **reducing the number/frequency of safety assessments to a minimum essential level** to limit patient contact during the COVID-19 pandemic?

- What is the regulatory perspective on **risk-based changes to safety monitoring** (i.e., reducing the frequency of vital sign measurements if there is no vital signs safety signal in previous studies)?

- Contact Research Organizations are starting to invoke '**force majeure**' clauses and **refuse in-person monitoring**. How will regulators see **compliance** when monitoring may be **exclusively remote**?

- Do FDA and EMA feel that **telemedicine visits** are sufficient to ensure patient safety in lieu of in-person visits with physicians during clinical trials? If not, could **local physicians** be employed by clinical trial sites to perform **in-home visits** while the **prescribing doctor remains the Principal Investigator**?

- In the context of COVID-19-related protocol changes, what is the regulatory perspective on **accepting safety assessments from community instruments**, which may not have the same calibration records and specifications as the original study center instruments?

Safety data interpretation and future labeling

- If clinical trial participants unfortunately become ill with COVID-19, they may experience more adverse events that they would otherwise. How will known **COVID-19 symptoms** be separated from those that are **likely or probably related to the study drug**, for the purpose of **future drug labeling**?

Changes to the statistical analysis plan

- Can a **blinded analysis** of data from a study currently underway be used, in consultation with the Agency, to **refine the final analytic plan** and potentially **change the primary endpoint**?

- Can an ad hoc (**not pre-planned** in the protocol), **unblinded interim analysis** be used for **sample size re-estimation** in case of large scale missed assessments and/or missed treatment doses? Are methods such as **CHW** appropriate, provided all blinding integrity protection procedures are in place?

Regulatory processes

- In light of COVID-19 related changes in drug development, are there **any new mechanisms to discuss clinical strategy with EMA?**

- At **FDA**, have there been any **delays or other effects** for **non-COVID-19 NDA submissions**?

You are invited to continue our conversation during a chair hosted interactive Social Hour
2:15-3:15 pm EDT

Return to the Lobby or Agenda to enter an interactive Social Hour with ISCTM colleagues

Next Session
11:45 am EDT

Special challenges in pediatric drug development

Access the session from the Agenda or Lobby