Rare Disease Forum
Conducting Clinical Trials Amid COVID-19 (Rapid Action Group)
Web Discussion 2: Summary Notes
July 9, 2020

I. DISCUSSION TOPIC

- The purpose of this discussion is to understand the statistical considerations due to the impact of COVID-19 on conducting clinical trials and to discuss the FDA *Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency* as it applies to rare diseases.

II. FDA STATISTICAL CONSIDERATIONS FOR CLINICAL TRIALS DURING THE COVID-19 PUBLIC HEALTH EMERGENCY

- Published in June 2020, the guidance addresses statistical considerations for changes proposed in clinical trial conduct that may impact the analysis and interpretation of primary or key secondary endpoints. It is intended to remain effective only for the duration of the COVID-19 public health emergency. The guidance focuses on ways to ensure trial integrity, and it includes possible trial mitigation and analysis strategies. Sponsors are recommended to consult with the appropriate FDA review division when considering changes to the trial protocol and statistical analysis plan.

III. PANELIST DISCUSSION

Disclaimer: The discussion represents the panelist's own perspectives and experiences.

- **Question: How has the pandemic and lock down affected the overall health of clinical trial participants and how do we account for this in the analysis?**
  - Due to the pandemic, patients in clinical trials may experience changes in diet, concomitant medication, and daily life practices that differ by region and other risk factors. These changes may or may not impact the primary endpoint. However, if these factors do affect the endpoint, the challenge becomes how to account for this in final analysis and interpretation of trial results.
  - From a clinical perspective, the health of patients with rare diseases can worsen due to an intercurrent illness, putting them at a significant level of risk. Exposure to an infectious agent introduces risk that cannot be controlled for even in double blind placebo trials.
  - There is also risk involved with the implementation of a trial based on the type of intervention. For example, for gene therapy trials, an immunosuppressive regimen is given in the beginning to increase uptake of the therapy vector. During a pandemic, this is a significant risk factor for patients. How does one adequately recruit participants and impress the risk of immunosuppression on patients while being certain that the risk is justified in context of a pandemic?
    - The risk assessment may be different depending on the patient's condition. Some rare diseases are degenerative while others manifest chronically over 10-20 years. For the former group of patients, the risk of delaying a gene therapy clinical trial that has the potential to stabilize or improve the patient's condition is different and may be more acceptable than in the latter group of patients. For patients with chronic conditions, one should consider if it will make a difference to enroll patients now compared to one year from now. If not, delaying the trial should be considered.
  - For trials with imaging or histology-based endpoints, visiting the investigational site poses a risk for patients, especially for those who are immunocompromised. Based on the health of the patient and other existing comorbidities, their overall risk for COVID-19 disease progression may be higher. Currently, there is uncertainty regarding the impact of

a SARS-CoV-2 infection on a specific existing condition and how disease trajectories are changed under different circumstances.

- **Question: How do we account for the pandemic in the trial analysis? What is the estimand in question we want to address?**
  - The estimand framework provides a way to formalize intercurrent events. It is important to collect data that may impact the outcomes; this may require an amendment in data collection or the CRF. It is also important to identify the percentage of patients experiencing the intercurrent event and the overall impact on the trial.
  - Analysis considerations should be made on a case by case basis because it is dependent on specific COVID-19 related intercurrent events. Appropriate summary, sensitivity, and supplemental analyses should be performed to address the estimand in question and the effect of intercurrent event.
  - In addition to changes in daily life, examples of intercurrent events that may be experienced by trial participants include changes in participant adherence to study treatment, treatment discontinuation, temporary treatment interruption, changes in concomitant medication, delayed treatment supply, site/region specific issues, and problems with treatment administration.
    - In relation to COVID-19, examples of intercurrent events include infection with SARS-CoV-2, hospitalization and other factors related to a participant's ICU experience, administration of an experimental COVID-19 treatment, and terminal events.
  - Due to the changing health status of the patient population during the trial, one should evaluate if the investigation is addressing same clinical question that it was intended to answer based on the primary endpoint and the corresponding primary estimand.
    - Additionally, changes in patient enrollment may result in differences compared to the target patient population. For example, individuals who are at a higher risk for COVID-19 may not enroll in the trial, which will affect the treatment component and the evaluation of the variables and primary endpoints.
  - If the patient populations behaved differently, is it appropriate to pool the population together when using a treatment policy approach? Should other approaches and/or covariate adjustments be considered?
    - Applying a treatment policy strategy that ignores the impact of COVID-19 would not reflect the real world because patients would not normally have these experiences in a post-pandemic setting.
    - Applying a composite strategy with endpoints that takes into consideration the intercurrent event is problematic from an analyst perspective because it does not reflect general practice in a post-pandemic setting.
    - Similar concerns apply when considering the principal stratification strategy.
    - When applying a hypothetical strategy, the question to consider is what the outcome would be if the treatment continued as planned. If there is not a lot of missingness, using a hypothetical estimand may be the preferred strategy because there are currently many unknowns about how COVID-19 impacts existing comorbidities and how the disease course is changing.
  - Both interventional and non-interventional data should continue to be collected in areas without well-established standards of care treatment to better understand how to address the impact of the pandemic in the analysis.
  - Generally, it is not recommended to end a phase III trial early because it can lead to inconclusive or erroneous decisions due to the lack of information needed to evaluate the success of an investigational product, unless a Bayesian framework is applied in order to consider existing/historical data.

- For missing data, it is important to consider what assumptions are applicable in each situation. For example, data can be considered missing completely at random (MCAR) if the data is not dependent on the treatment and outcome (i.e. missing data is site dependent or pertains to a specific time period during the pandemic). However, if the missing data is excluded from the analysis, the loss in statistical power will be hard to mitigate for rare disease trials with small sample sizes.
  - Possible considerations to compensate for this loss in power include extending the enrollment period and recruiting more participants, using historical data, applying missing at random (MAR) assumptions, or using a mixed effect model approach in the analysis.
  - Other factors to consider include time-to-event data and competing risks.
- It is important to try to keep the primary analysis unchanged if possible, especially for confirmatory trials. However, if the pandemic has significantly impacted the trial and a large number of the participants, then modifications to the primary analysis may be needed. This should be discussed with the regulatory authorities.
  - Any data collected during pandemic needs to be compatible with data collected in a post-pandemic setting. This should be clearly stated in analysis plan.
  - Corresponding and appropriate primary, sensitivity, and supplemental analysis plans need to reflect the impact of the pandemic before locking the database.
  - The impact of the pandemic on labels have not been determined because trials are still ongoing.

- **Question: Does the new FDA Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency provide adequate guidance for trials in rare disease? If not, what is missing?**
  - The FDA guidance contains good advice on this topic, and the agency has been communicative regarding their advice. Regulatory agencies should be commended for their flexibility and response time during the pandemic. Agencies will continue to update their guidance as they learn more.
  - Issues that were not address by the FDA guidance in regards to rare diseases trials.
    - For small trials, the guidance needs to further discuss the issue of compensating for statistical power, interim analyses, and stopping a trial early.
    - From a clinical perspective, rare disease patients are doing better during pandemic because they are taking better care of themselves and protecting themselves from exposure to other risks/illnesses by sheltering in place. Therefore, if the control group is doing better, this may disguise the effect of the drug compared to a non-pandemic setting.
    - Alternatively, given the risk of exposure to SARS-CoV-2, an investigational product may work but the treatment effect may be difficult to detect because the population as a whole is sicker than they would have been in a non-pandemic setting.
    - For rare disease trials, the use of external/historical controls instead of internal controls is common. However, due to the impact of the pandemic, these controls may no longer be valid because the course of the disease is now different.
    - There is a possibility of an inadvertent/unrecognized bias. If an investigational product is working and patient feels better, the likelihood of the participant continuing in a trial with the increased risks is greater than if drug is not working and if the patient does not feel better. Additionally, given that rare disease trials are often unblinded, participants in the placebo group may be more likely to withdraw. Thus, there is a bias introduced in favor of people who are seeing a benefit.

IV. ADDITIONAL INFORMATION

- Before making decisions and modifying design of existing trials, it is important to remember that our first assumptions may not be correct. Assumptions will change with time and with the evolving environment because there are currently many unknowns regarding SARS-CoV-2 and its effect on the population.
- There are numerous publications and discussions that took place within the last month on the statistical considerations of conducting clinical trials during the pandemic with many overlap ideas. This a positive indication that everyone is thinking along the same lines. Many publications are more general and not specific to rare diseases.
- Because the issues and impact of the pandemic are still evolving, industry, academia, and regulatory authorities do not know everything at this moment. No single document/guidance has all the information. Currently, individuals are anticipating changes and concerns based on what has been observed, but more may be seen with in due time.

V. QUESTION & ANSWER SESSION

- **Question:** Are there any methodological agreements on how to address changes to the primary or key secondary endpoint when the trial is already halfway completed in order to analyze the data and reach a conclusion? For example, a study replaces a 6-minute walking test that is usually conducted at the investigational site with an assessment that is now completed at home with a wearable device due to the pandemic.
  Response: In rare disease trials with small sample sizes, modifications to primary or key secondary endpoints can be problematic because the change in most therapies can be relatively small, meaning that the result may not be statistically significant. Additionally, if the substitute endpoint that is being considered is an appropriate and valid endpoint, then it would have been included in the original trial. Thus, if there are concerns regarding the substitute endpoint (i.e. it is not well recognized or not easily standardized), then it may not be an appropriate endpoint to include without exploratory work to demonstrate its validity. Perhaps one can consider delaying the endpoint ascertainment instead of changing the endpoint.
- **Question:** Given the uncertainty about the duration of the pandemic, when substantial amendments are made on the conduct of the trial, should these changes be transient (with risk of a second wave and another locked-down period) or should the changes be applied until the end of the trial?
  Response: It depends on adaption, our knowledge on the measurement, and how intercurrent events are addressed in the trial. For global trials, conditions will never be the same for every part of the world. A discussion with regulatory agencies may be warranted if there are confounding factors that will impact the adaptation if you revert back to "normal." When considering a principal stratification strategy, data analysis is easier if changes are implemented once, instead of multiple times. Having multiple infection points may create more complexity and confounding, resulting in uninterpretable trial results. Therefore, if a change needs to be implemented, make the change once and keep it until the end of the study to minimize its effect on trial conduct. Ultimately, this decision will depend on impact and the complexity of the situation.
  For regulatory compliance, adaptations need to be implemented before unblinding to minimize bias. In the case of rare diseases trials, these trials are usually unblinded to begin with.
- **Question:** When assessing the impact of COVID-19, how do we determine the impact period (the beginning and the end) of the pandemic? As we continue to learn about the impact of COVID-19, data collection for COVID-19 related factors may not be complete and/or unreliable, especially when factors that were not obviously related turn out to be significant after the recording period has passed. How do we address this?

Response: Due to regional differences, it will be difficult to determine the impact period, especially for global trials. It may be preferred to wait until you are certain about the impact and the impact period before making changes to the trial at the end or during an interim analysis. A general rule is to make changes before locking the database.
Additionally, it is important to keep the primary analysis and determine what you know and what is clinically interpretable. If a post-baseline factor is impacting the trial, a general strategy is to propose an analysis plan (such as a principal stratification strategy) based on information from literature and from different academic societies. In situations where you do not know the cause and effect of the intercurrent events, one should not alter the primary analysis and instead include supplementary estimands to address the situation that is observed. During the pandemic, there is greater flexibility from IRBs and investigational sites to implement changes without waiting for an amendment as long as there is agreement on what changes are needed. However, it is also important to keep in mind that we will exit from the pandemic eventually.
From an implementation perspective, clinical trial staff are well trained on collecting data on factors that impact health, including unexpected factors. The possibility of missing information because we do not know what we are looking for exists, but there is a good possibility that staff members will recognize major factors that surface relative to an unanticipated factor, like a pandemic.

- **Question:** For rare disease patients enrolled in a clinical trial who might have been infected with SARS-CoV-2 and treated with experimental products for COVID-19, is it general practice to exclude them from the clinical trial for their rare disease?
- **Question:** Will there be consequences on the quality of data in natural disease history studies collected during the pandemic and/or lock-down period? Will future comparisons and use of these natural history data be affected? The FDA guidance addresses the impact and changes in clinical trials, but not in other studies such as natural disease history and the integrity of data collect.

VI. TOPICS FOR UPCOMING WEB DISCUSSION 3

- For clinical trial on rare diseases (which generally have smaller sample sizes), what is the impact of intercurrent events and missing data on statistical power?
- Is it appropriate to use historical and external controls in rare disease clinical trials conducted during the pandemic?
- How will data from natural disease history studies that are currently conducted during the pandemic be used in the future?