Rare Disease Forum
Conducting Clinical Trials Amid COVID-19 (Rapid Action Group)
Web Discussion 1: Summary Notes
May 15, 2020

I. MAIN DISCUSSIONS

- The purpose of this discussion is to understand the challenges that currently surround conducting clinical trials during a pandemic, and approaches to these challenges (how to move toward decentralized trials, while maintaining efficiency, patient safety, and data integrity) while laying the groundwork for transforming the rare diseases clinical research paradigm to be more patient friendly and efficient for the future.

- Steps taken to include the overall safety of patients during this time:
  - Sent out blood pressure monitoring machines for patients with hypertension so that patients can monitor from home. For data integrity, they have ensured that the appropriate information gets sent to the central lab.
  - Oversupplied patients with drugs in case they miss a visit.

- What is the best way to handle data in different situations? In terms of clinical trials, since COVID-19, there has been in impact in both the design and analysis perspective.
  - There have been many interruptions in visits which has caused a loss in information. Can we treat this as an interim analysis and potentially enroll additional patients later on? Can we bring in external data? Can we bring virtual control features into the design? In the analysis aspect, at the end of the study, we will want to know if the data is still consistent (several features include: population treatment variable, current event, and summary level report)?
  - Have you kept the same treatment paradigm that you had at the beginning when you defined your primary estimand for the trial?
  - Where are the missing values coming from? Can we use a "missing completely" strategy and exclude them? If this is not the case, what kind of supplemental strategy do we need to bring into the protocol so that we can still have a robust primary analysis and infer what we intend to do with the drugs for this disease area?

- Some organizations have redirected their staff to work specifically on COVID-19 trials right now (especially for high-risk ventilated patients using stem cells).
  - Some clinical trials have been able to continue during this time and are in follow-up. Specifically, for the trials in follow-up, telemedicine has been utilized, equipment has been sent to patients' homes, and the information has been recorded with a physician or PH at hand via telemedicine.

- Rare disease studies are geographically dispersed across the country with few of them that require travel for subjects, making it difficult for subjects to come in to get a certain procedure done that can't be skipped.
  - There's a subset of trials that will be impacted more and those are trials that involve therapies that are going to put subjects at increased risk (e.g. gene therapy).
  - The final impact of running these clinical trial programs during this time is the effect it has on personnel.

- There has been an impact of COVID-19 with interrupting trials, stopping enrollment, termination of studies, interruption of clinical supply in the middle of a trial, and incomplete longitudinal data collection (where endpoints are measured by repeat site visits).
    - If the interim analysis hasn't been done, you have an opportunity to examine other data sources (such as registry data and competitor data). If there is interim analysis data, you can use that data to help inform where to go next.
    - There are certain methods that can be applied when thinking about missing data. Mathematical model-based methods can be used to analyze data. You can potentially make decisions from earlier time points in a longitudinal study and try to make projections by pulling in prior information with Bayesian data analysis methods.

- Metabolic patients typically go to school/work during viral flu and cold season and are exposed to environmental pathogens and other health-affecting agents. This leads to sickness requiring a visit and record in the CRF. Of interest, we are seeing a decrease in hospitalizations for patient in studies as well as general clinical improvement, potentially because patients (e.g. PKU) are controlling enzyme levels better since they are not at school and the usual "out of the house" temptations are diminished. This would be a pre-post COVID-19 situation, as referred to earlier. Normally, in a randomized trial, this might be considered a placebo effect (assuming this effect is happening in all arms). But in this situation, the improvement in clinical presentation can be large enough to mask the drug intervention effect.
    - If a patient typically has 12 clinical visits in a year, visits may be decreased to four per year with treatment. As a result of the COVID-19 pandemic, federal and state governments have been implementing various social distancing measures. These distancing measures seem to have a greater effect on the patient than the therapeutic effect. Therefore, patients may only need three clinical visits per year with the presence of social distancing. In this situation, the therapeutic effect has been missed because the primary risk factors have been eliminated.

II. ADDITIONAL QUESTIONS

- **Question**: Is there anybody on the call who has already communicated with the FDA or for that matter, also with the European Agency?
  Response: The FDA has been very responsive to adjusting the clinical trials with the intent of maintaining statistical significance and the endpoints that were once generated. Marc did a nice job of mentioning interim data analysis to determine if clinical trials really needed to continue. That's one of the strategies. But as far as the FDA goes, outside of the COVID trials, they had been more than accommodating and accepting of various technologies and tools to ensure good solid data is being generated.
- **Question**: How are registries being affected if they are prospectively collecting data (since patients are not able to come into the clinic)? - This is a question that the group should keep on their radar and come back to.
- **Question**: I'm interested to know if anyone has done any initial surveying/interviews with patients and families currently in trials on their opinions about risk and needs (food insecurity, lack of in-home care, changes in living arrangements, willingness to continue trials amid COVID-19, etc.).

III. TOPICS FOR UPCOMING WEB DISCUSSION 2

- Analysis/estimands: How has COVID-19 affected the overall health of people and how do we analyze/interpret this information?

- With many patients doing better, how do we determine the effect of the treatment in randomized trials?
- In order to make trials decentralized, how is remote monitoring being used/how can remote monitoring be used? What tools should be used for remote monitoring?
- Loss of personnel.