CONSIDERATIONS FOR THE NEXT WAVE OF COVID-19 DEVELOPMENT

The onset of the novel coronavirus pandemic created a global health emergency and a rush by the biopharmaceutical industry to develop novel therapeutics. The next wave of development will come from sponsors observing the evolving situation and making their contribution in the fight against the virus (COVID-19).

The Coronavirus pandemic is a global medical threat with an urgent unmet need for therapeutics. Recently, there has been a large number of collaborations across the therapeutic development landscape at the regulatory, operational and business-transaction level. "What would usually have taken months of negotiation is now being signed off and finalized in just a matter of days to a few weeks", says Brian Murphy, Vice-President of the medical department at Medpace, a trend that he says shows no signs of slowing down.

As of June 2020, there are over 2,000 COVID-19 studies on the government's clinical trials database, and over 3,400 on the World Health Organization's (WHO) database, with numbers growing on a daily basis. They are being supported by a flood of funding from biotech venture money. Murphy estimates that the figure is approximately 5 billion dollars in just the first quarter of 2020.

The key element to consider with time-sensitive drug development, such as with the case of the coronavirus pandemic, is the need to ensure that decisions are being made quickly as well as carefully. Regulatory agencies have all been amenable to moving quickly in this scenario, but not to the point of taking shortcuts that may increase safety risks for clinical trial participants.

CHARACTERISTICS THAT DEFINE A COVID-19 CASE

There has been a certain degree of difficulty with defining a coronavirus case. When clinical trials began, few COVID-19 tests were available, and patients were being admitted to trials based on exposure history and symptoms. However, PCR-based tests are now more readily available, and participants can be confirmed to have the coronavirus before being admitted to a study. So, for treatment trials, sponsors are now documenting the diagnosis of COVID-19 as a laboratory-confirmed disease, since PCR testing or antigen testing can now be obtained.

Sponsors also need to consider the inclusion criteria and defined endpoints for COVID-19 patients. The coronavirus causes disease with varying degrees of severity. Some patients have mild symptoms or are asymptomatic. Others need to be placed on ventilators due to respiratory distress, and those with respiratory failure require mechanical ventilation. Non-respiratory events of disease progression must be evaluated as well, including kidney coagulopathy.

Regulatory agencies must be aware that the definition of cases evolves along the spectrum of severity, and they must consider their product's safety profile, and whether or not it is appropriate for a given trial participant, according to the state and severity of the infection. Novel drugs are expected to be safer for patients in the early stages of infection, while patients in later stages may have higher acceptable levels of risk, if all conventional treatments have failed. Many sponsors are interested in clinical trials for COVID-19 patients testing drugs that have already been studied in other patient populations. However, the metabolism of the drug may be different in coronavirus patients, especially those who have hyperactive immune systems.

STUDY SIZE

Study size is a critical component of clinical trial design. The size of the study must be discussed with regulatory agencies within the context of the study goals and the stage of development. A proof-of-concept study needs to be considered in terms of what phase it is in, and whether there are adaptive elements. There is a need to move into the clinical phase quickly, a concept that is understood by both researchers and regulators.

Sponsors may feel pressed to move out of animal models to patients or healthy volunteers as soon as possible. As a result, in some situations, even though the regulatory requirements are met, there is still limited information on the efficacy of the product based on the animal model. In this case, small trials, such as pilot and proof-of-concept studies are advisable.

ADAPTIVE DESIGN

Given how quickly the coronavirus pandemic has changed and the standard of care, many clinical trials have seen a number of adaptive elements. Clinical trials may have been stopped early due to either futility or overwhelming efficacy, in which case the sponsors have expanded from a proof-of-concept study to a large confirmatory study. Clinical trials have also seen adaptations such as sample size re-adjustment. Sample sizes are determined a priori in the trial protocol with oversight from independent data monitoring committees. Statisticians inform sponsors of the status of the data in order to keep the type I error rate under control. Typically, the sample size will be increased to improve the statistical power of the study result, with the goal of moving the trial to a registration study as soon as possible.

There are also studies that have reduced the overall anticipated final sample size. At least for some trials, this has been due to a reduced number of COVID-19 cases available in the defined study population. Sample size reductions must always be discussed with regulatory agencies, and they will expect to see evidence of some effort to expand the study to additional sites. The region of the study population may be expanded to meet the necessary sample sizes. Expanding enrollment time can also increase sample size, but typically costs more money, so the cost must be weighed against the potential risk of interpreting results from studies that haven't met their target enrollment or statistical significance.

Regulatory agencies have an understanding that there are fluctuations in the incidence of COVID-19 between different geographical regions. Events outside of an ongoing trial may need to be considered in the revision of a trial design or an amendment of its protocol. These revisions must be justified in order to ensure that sponsors are not taking shortcuts. Regulatory agencies will be holding to their standard expectations, despite the expedited drug development process for coronavirus therapeutics.

"We are starting to see agencies saying, 'your 15-patient proof-of-concept study is not going to cut it'. So, it's probably better at this stage to look at describing an adaptive design that would move you from dose escalation with some sentinel core, depending on what your safety profile looks like, to the next stage of a larger trial", says Hervé Momméja-Marin, Vice-President of the medical department at Medpace. Momméja-Marin explains that clinical trials with adaptive designs will have a greater chance of being reviewed and approved by regulatory agencies. He also explains how regulatory agencies may favor trials that have more participants, and therefore larger sample sizes and greater statistical power. The term 'adaptive' is broad. In the clinical trials context, it refers to a continuous data review process involving the re-assessment of factors such as sample sizes, as well as the potential modification of endpoints.

COMPARATORS

There is still no widely available comparator that is fully approved for COVID-19 patients, and the best available therapy may vary regionally, depending on the severity of the patient. The background standard of care should be the same in both treatment arms, and a number of medications are being used off-label, since researchers are still working to fully understand the coronavirus disease. Since that is the case, there have been discussions around single-arm trials of the investigative product. However, such trials are unlikely to be accepted, as the disease's natural history is still not completely known. The current state of clinical trials is the placebo-controlled trials. They are the most common and are what is expected from most regulators at this point in time.

The appropriateness of using off-label drugs for clinical trials of COVID-19 therapeutics depends on the mechanism of action of the drug. For example, an antiviral drug would not be approved for a trial of antibiotic potency. In addition, regulators want to see an incremental benefit compared to the current standard of care.

While the coronavirus studies are moving at an accelerated pace, there are no shortcuts to a high-quality clinical trial. Additionally, flexibility must be built into the protocols as it allows for clinical trials to adapt to the rapidly evolving pandemic. Standards of care may change and therefore require adaptations to the trial protocols. It is also important to work with regulatory agencies as much as possible, as they are readily engaged and encourage sponsors to reach out for advice sooner rather than later in the trial design process.

APPROPRIATE ENDPOINTS FOR COVID-19 INDICATIONS

An important component of a successful clinical trial is to select the right efficacy endpoints. The Federal Drug Administration (FDA) released their guidance for developing drugs and biologics for COVID-19 treatment and prevention in May of 2020. In that document, the agency proposes key recommendations for selecting proper endpoints in any drug development program for drugs to treat or prevent COVID-19. There are three main factors to consider. The first is the population under study, the second is the clinical setting, whether the patients are outpatients or are hospitalized or are in the intensive care unit (ICU), and the third is the baseline severity criteria for the disease. These factors are closely related to each other, so the key message from the FDA is that the interpretation of endpoints may differ, depending on the population evaluated in the trial. So, the agency is emphasising the importance of differentiating between different patient populations. Another key message is that early interaction and collaboration with regulatory agencies to discuss appropriate endpoints for the study is of paramount importance for the sponsor and the CRO.

The identification of risk factors for the progression of disease is useful for the study design, as well as defining the population to be included, and also for patient stratification. Until recently, the identified risk factors for severe illness or death from COVID-19 have been the age of the patient, the presence of underlying comorbidities and the status of certain biomarkers. A study from the United States suggests that the case fatality rate was highest (10-57%) in people who were at least 85 years old and was lower (<1%) for people younger than 55. There is therefore a large difference in the presence of underlying comorbidities that are related to poor outcomes. Other risk-enhancing comorbidities include cardiovascular or respiratory diseases, diabetes mellitus, chronic kidney disease or any condition that leaves a patient immuno-compromised.

COVID-19 has also been associated with many inflammatory changes, including ischemic complication, coagulation disorders and endotheliitis. Systemic vasculitis and cytokine-mediated coagulation disorders are principal actors of multi-organ failure in patients with severe cases of COVID-19. Several biomarkers have been evaluated to help predict disease outcomes. The biomarkers can be classified in terms of their relationship to poor prognoses. For example, the lymphocyte count, neutrophil count, and neutrophil:lymphocyte count ratio. Some other biomarkers are inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate, and procalcitonin. Others are immunological, including interleukin-6 levels, and still others are biochemical, as in the case of d-dimer troponin creatine kinases and transaminases.

New Laboratory biomarkers may be identified through the accurate analysis of multicentric case series. For example, homocysteine and angiogenesis have been suggested as potential biomarkers. Some examples of important clinical outcome measures used in COVID-19 treatment trials are all-cause mortality, the presence of respiratory failure, the need for invasive or non-invasive mechanical ventilation, and the need for ICU level care or hospitalization. Clinical outcomes can also be measured in terms of sustained improvement, such as the return to room air and baseline oxygen requirement.

The most common endpoints used in clinical trials of patients with severe or critical COVID-19 include all-cause mortality at an appropriate time point, usually 28 days. Other common secondary endpoints include the proportion of patients alive and free of respiratory failure, and a clinical status evaluation. Clinical status is usually evaluated using a scale that incorporates multiple clinical outcomes of interest: death, mechanical ventilation, etc., ordered by their clinical importance. The final endpoint is the time to sustained recovery, where recovery is assessed over an appropriate duration.

Another important factor to be considered is the duration of the clinical trial. The FDA recommends that sponsors address potential relapses in their endpoint definitions to ensure the adequate assessment of the durability of the response to therapies. Therefore, the trial should be of sufficient duration to ensure safety and effectiveness of the therapeutic being evaluated. For example, a four-week clinical trial will likely be sufficient to capture most important outcomes of mortality in a trial of mechanically-ventilated patients. Longer durations would be appropriate for trials of patients who are less ill at baseline and for trials of preventative treatments. In some cases, longer follow-ups should be considered to assess safety.

It is also important to consider whether COVID-19 is milder in persons receiving prophylaxis compared with those not receiving it. Data on symptoms and hospitalization rates must be collected in order to support an analysis of that nature. “I anticipate that as the pandemic moves along and there are more clinical trials being run on COVID-19, that agencies are going to move towards more traditional endpoints, such as all-cause mortality”, says Dr. Anibal Calmaggi. He also predicts a growing interest in populations that have been excluded from the initial COVID-19 trials. For example, patients with renal impairment, who make up a significant portion of COVID-19 patients but may respond differently to therapeutics or be more vulnerable to their side effects. Other commonly-excluded groups include pregnant women and children. Dr. Calmaggi recommends engaging in conversations with regulatory agencies in order to determine appropriate trial endpoints. He explains that collaborating with regulators is a powerful way to optimize a clinical trial, as they understand that there is a great need for novel therapeutics on short timelines in response to the COVID-19 pandemic.

CONCLUSIONS

The COVID-19 clinical trial space is an evolving dynamic environment, as described by Carrie Sheil, the Senior Director of Clinical Trial Management at Medpace. “Reviewing trends and daily analytics allows us to navigate the competitive landscape”, she explains, “We’re going to continue to see differences across countries in the potential second wave”. Ms. Sheil says that careful planning and having contingencies in place, as well as careful assessment of the status of clinical trial sites will allow sponsors to mitigate the restrictions and help support the site in continuing to recruit trial participants.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace’s mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.