OPERATIONAL STRATEGIES FOR SUCCESS IN COMPLEX OPHTHALMOLOGY CLINICAL TRIALS

With recent and promising advances in ophthalmology drug development, the management of ophthalmology clinical trials is becoming increasingly complex. Not only is it important to have ongoing guidance from embedded medical expertise at every step of the trial, it is also critical to have the operational know-how and experience to successfully execute a complex ophthalmology study. Medpace's expertise and experience in leading complex ophthalmology studies and consistent track record of success enable our team to adapt to the unique challenges of each ophthalmology trial.

Some common considerations include the availability of adequate site resources, equipment, vendor management, lab collection logistics, training of investigators, challenges with patient recruitment and retention, as well as additional levels of complexity associated with gene therapy and rare disease trials. To succeed in ophthalmology clinical development, it is essential to understand these common considerations and operational strategies for success to accelerate the path to approval. In this article, Medpace Clinical Operations leaders share key considerations for navigating some of the complexities of ophthalmologic clinical development.

SITE CONSIDERATIONS

Sourcing the Necessary Equipment

Ophthalmology sites often don't have all the necessary equipment on hand that may be required for research studies beyond common ophthalmology-specific equipment. To be successful, the study team must assess the sites to evaluate whether they have the required equipment, typically during the feasibility process.

The Medpace vendor management group can assist sites in sourcing specific equipment required for protocol-required study procedures. For example, sites may not have specific equipment to capture required images such as microperimter, -70 degree freezers for lab sample storage, protocol required visual acuity charts, etc. In those cases, vendor management and Medpace logistics will work to source the necessary equipment for the sites to successfully conduct the study.

Oftentimes, especially within the US, clinics use an ambulatory surgical center. Depending on the process for the IP, especially for a gene therapy to be transferred to the surgical center, the gene therapy must be stored at

less than -80 or -70 degrees. They may have a freezer in their surgical center but may need another within their clinic for the storage of lab samples. In some ophthalmology studies when the sponsor is using an outside surgical center, they may have a freezer in one place but not the other and as a result, the sponsor must provide that to the sites.

Accommodating Mobility Testing

A multi-luminance mobility test (MLMT) is a standardized, lab-based test used in ophthalmology clinical trials primarily as a visual functional assessment. In a mobility test, the patient is asked to navigate a course and is evaluated on the time it takes to complete the course and the number of obstacles hit along the way. A baseline measurement is taken prior to administration of the IP, and then additional measurements are taken to determine if the therapeutic has any impact on visual function. Studies are starting to have these courses validated and use them as a standard assessment for visual function through the FDA. For example, mobility testing has been validated for leber congenital amaurosis studies and retinitis pigmentosa studies. Sponsors are including these functional visual assessments as a study component at an increasing rate, bringing about additional considerations for feasibility and site selection.

When an MLMT is required, one of the most common challenges faced is finding enough space at the investigator site to conduct it. Because mobility testing is primarily used as a visual functional assessment in clinical research, a typical ophthalmology site will not have a course set up at their facility, nor will they have adequate space available to construct the course. The minimum space requirement for a mobility test is about a 14’ by 20’ footprint, per ORA specifications. Ideally, the space should be larger to accommodate a table to accommodate site staff for observation and note-taking.

In rare instances, sites that are already participating in clinical studies may have an existing mobility course set up and can utilize the existing space for an additional study. Identifying and selecting these sites for a study that will require a mobility test can remove some of the additional complexity associated with mobility testing, however, these instances are rare.

Medpace has had a lot of recent experience helping sites find and lease a suitable space, so we're becoming increasingly aware of strategies to manage this and look at space blueprints to point out what may be unsuitable about a space. We can advise sites on how to effectively manage a lease, drawing from our past experiences with sites that have been successful.

Lab Collection Challenges

Lab collections must also be considered with ophthalmology sites. Almost all ophthalmology studies require lab collections, but the lab collections are not typically completed as part of ophthalmology standard of practice. There may be a phlebotomist on site, but if not, support may be needed to identify local labs.

Ophthalmology sites that do not have experience working with a local lab can often be hesitant to contract and set up agreements. Not all sites are willing to contract with local labs, which limits the number of sites that can be selected, and the quality of the sites becomes a challenge. To alleviate these concerns and simplify the management of lab collection and logistics, Medpace recommends using a central lab to support ophthalmology studies.

Using a central lab eliminates the need for the site to set up and manage an agreement with a local lab, reducing paperwork and administrative burden for the site. A site doesn't have to reach out to a local lab to obtain a confidentiality agreement or a contract with the local lab. It's easier for sites to collect the sample, ship it to a central lab, and receive results directly from the central lab as results are populated to the study directly with immediate access, eliminating the administrative burden of manually entering all the lab results into the EDC system.

Vendor Management

For natural history or observational studies, or in some cases phase 1 studies, the sponsor may not want to utilize an outside vendor for a lane certification. As a study progresses to phase 2 or phase 3, lane certifications are required by the regulatory authorities and bring about additional operational considerations.

An outside vendor is typically required to qualify the lane where the visual acuity assessment will be completed, ensuring proper distance and equipment are available to carry out the assessment. Vendors can also certify the technicians who will administer visual acuity assessments, ensuring proper training on manifest refraction. Since a visual acuity assessment is dependent on judgment from the specific technician who will administer the assessment, they are considered subjective to some degree. Fluctuations in biases from different technicians can trigger a significant change in a visual acuity assessment if not managed appropriately with adequate training. One strategy to decrease the impact of subjectivity and ensure consistency of results is to have the same technician conduct all visual acuity assessments for an individual patient for the duration of the study whenever possible.

Vendors will typically provide sites with a study reference manual or study training and creating site training documents can also eliminate disparities. The reference manual is a step-by-step guide that is required for not only the lane certification and setting up of the equipment, but the visual acuity assessments themselves. The manual is always available to reference and to use to train additional staff, which helps to create standardization and consistency across individual technicians and sites.

Medpace has developed robust internal processes informed by our experience executing complex studies that require vendor management. The vendor management group at Medpace helps to ensure that the study team is selecting and contracting with the right vendors for the study from an operations and contracting perspective.

CONSIDERATIONS FOR GENE THERAPY AND RARE OPHTHALMOLOGY TRIALS

Gene Therapy Challenges

Gene therapy in ophthalmology trials is becoming increasingly common, bringing about additional complexities to consider. Some of the biggest challenges for gene therapy in ophthalmology trials include storing the sample, ensuring sites are properly trained on dosing and ensuring study procedures and assessments are followed to ensure potential AEs related to the gene therapy are identified.

"Medpace has dedicated medical and operational leadership for ophthalmology, and a significant amount of gene therapy experience. In fact, we don't really consider gene therapy a challenge because it has become the norm for us. We have experience with many of these ophthalmic indications, especially the retinal ones."

Many sponsors are concerned with surgical training for delivering gene therapies in ophthalmology studies, for example, subretinal injection and vitrectomy. Subretinal injection can lead to variability, so it is critical that site staff are properly trained in administering the injection to ensure consistency.

Not only is it important for site staff to be trained on gene therapy, but patients must also be educated on the treatment to effectively enroll in the study. The patient recruitment and retention group at Medpace offers strategies and recommendations for sites on how to help patients understand gene therapy as well as ensure they are comfortable throughout the trial.

Educating patients on the gene therapy itself – how it works, the potential benefits, risks, side effects, and adverse events that may be associated – can help to ease any hesitation or discomfort a patient may have about participating in the trial. Educating the patients is one of the most important parts of gene therapy that can contribute to successful patient recruitment and retention.

Especially for pediatric gene therapy studies, developing a brochure or handbook geared for the child, as well as the caregiver, is an effective method to describe what is going to take place in a way that is easy to understand.

Once the study is underway, providing the pediatric population with a booklet they can use to track their journey through the study can be an effective way to keep them engaged in the trial. At the start of the study during the consenting process, it is imperative to ensure the site staff is utilizing these tools and are effectively explaining what is to be expected to both the patient and caregiver.

It is also important to explain the chance of being placed into the control group of a study and may not receive the IP. Stressing the importance of the control group and how it's going to be beneficial in the long term for patients who suffer from a particular indication is a way to overcome this concern in patients. In a completed study that is proved to be efficacious, it can be recommended to sponsors that patients in the control group have the possibility to receive the IP.

Feasibility & Recruitment Support for Rare Ophthalmology Trials

Many ophthalmology studies aim to treat rare diseases, which adds another level of difficulty to identifying and enrolling patients with a specific indication. Having relationships with KOLs within a particular indication is helpful in assessing where the patients are, which helps with recruitment. Medpace's recruitment and retention team support relationships with several patient advocacy groups to assist with recruiting for rare disease studies.

Even with these additional resources, it is often challenging to identify and recruit patients. Patients may not be located near sites and therefore must travel a far distance to participate in the study. Especially for rare diseases, it is important to ease the burden of participating in the study for the patient and provide resources to help them travel to a site. Medpace's Patient Concierge Services provides rare disease patients and their caregivers travel and financial support to help decrease that burden.

The Medpace Feasibility Group is also utilized to investigate indication incidence rates in certain areas for these rare populations. For example, indication rates would help discover where specific patients are located in a study focusing on fair-skinned, light hair, blue-eyed populations. The feasibility group finds where patients may be pocketed and then identify sites in those areas.

It is important in rare diseases to cast a wide net, meaning reaching out to several countries and several sites to identify where the best sites will be located. Although not ideal from a cost perspective, it is possible to have only one or two sites in a country, which is often the best way to recruit for a study to ensure different countries are involved. In some instances, there may be some countries that don't have a site participating in the study, but Patient Concierge Services supports relocating a patient to another country for the study.

The genetic component of an ophthalmic indication makes them rare in some instances in an ophthalmology gene therapy study since the patient must have a certain genetic defect. Some universities have collected an internal genetic database with a genetic profile over the years with their patients. That information on potential eligible patients is very useful during feasibility even though it may have been collected locally and will need to be confirmed via a central genetic lab. The databases give a good indication of how many individuals have a particular genetic mutation.

WHY MEDPACE

Understanding these and other common operational considerations of an ophthalmology clinical trial can help keep your trial on track and accelerate the path to approval. Medpace's cross-functional, collaborative model gives sponsors access to our ophthalmology-trained medical, operational and regulatory staff, as well as cross-therapeutic support. Our full-service model delivers efficient and streamlined execution and higher quality results. Contact us to learn more.