Innovations in ophthalmology clinical trials: medical, operational, regulatory and gene therapy considerations

This article will explore the intricate world of gene therapy in ophthalmology, highlighting the operational considerations and regulatory aspects of clinical trials in ophthalmology while delving into the science behind these transformative therapies

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The field of ophthalmology has long been dedicated to the pursuit of restoring and preserving vision, recognising that the gift of sight is one of humanity's most treasured assets. Yet the promise of clear and enduring sight has remained elusive for individuals grappling with retinal diseases, both hereditary and age-related. These conditions, often rooted in the intricate genetic make-up of the eye, can lead to progressive vision loss, eventually resulting in blindness.

Gene therapy in ophthalmology trials

In recent years, the convergence of genetic science and cutting-edge medical technology has given rise to a transformative solution: gene therapy. Gene therapy seeks to address the root causes of genetic disorders by repairing or replacing malfunctioning genes. In the context of ophthalmology, this revolutionary approach involves the introduction of functional genes within the eye, paving the way for restoration of visual function and offering new hope to those living with previously untreatable conditions.

The foundation of gene therapy in ophthalmology rests on understanding the genetic underpinnings of ocular diseases. Researchers have identified specific genes responsible for various vision-related disorders and have developed innovative techniques to correct or replace these faulty genes. By leveraging these advancements, ophthalmologists can potentially halt or reverse the progression of vision loss, providing patients with the prospect of improved sight and quality of life. Ophthalmic gene therapy innovation and R&D activities have rapidly increased in the last few years, with the number of ongoing and planned gene therapy studies ranking third after anti-diabetic and anti-glaucoma targeting drugs (**Figure 1**).[1] The promise of gene therapy is evidenced by the approval of Luxturna in 2017, a gene therapy for the treatment of RPE65 mutation-associated retinal dystrophy.[2] Currently, many gene therapy products are being developed for hereditary or genetically linked severe ocular diseases. Additionally, other innovative approaches, like RNA editing with antisense oligonucleotides, are under development.

Gene therapy is most effective for monogenetic diseases, where a known single mutation causes the disease, which is the case in many severe inherited retinal diseases. As innovation evolves, mutation agnostic gene therapies have also been developed for diseases caused

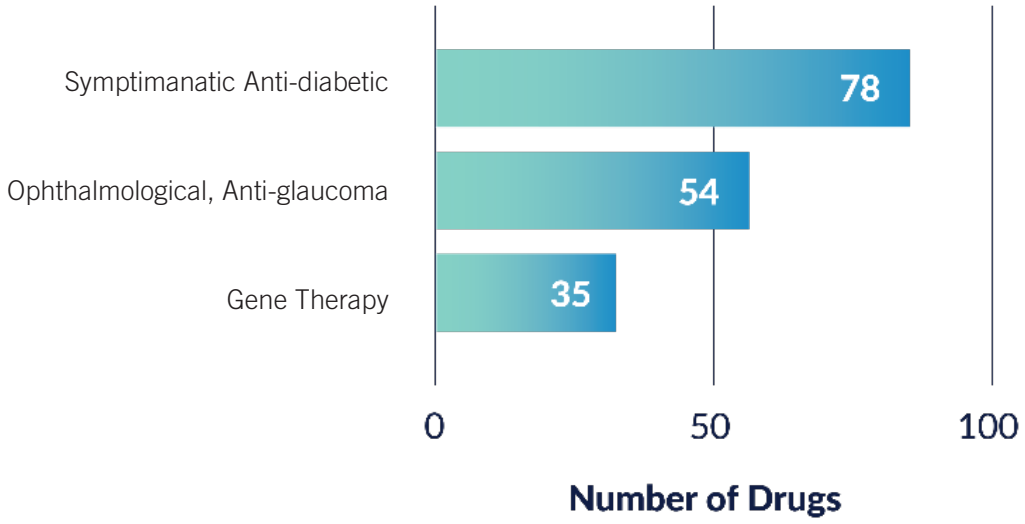

Figure 1: Drugs in development in ongoing or planned ophthalmology studies

by multiple mutations. A challenge of gene therapy is constructing the product and effectively delivering the functional gene. Most clinically used bio-engineered constructs consist of an adeno-associated viral (AAV) vector that contains the gene and an organ-specific promotor to infect and transduce cells for transgene expression. AAVs are harmless and common, and many people have been infected, resulting in developing antibodies against these viruses. Pre-existing neutralising antibodies against the treatment-specific AAV serotype may exclude patients from systemic treatment.

The eye is a small organ, and gene therapy for retinal diseases is delivered in the enclosed and immune-privileged subretinal space in a very small amount. Because of this, systemic exposure to the AAV vector and transduced protein is close to zero, and patients do not develop neutralising antibodies. An advantage of this is that the second eye can also be treated, unlike systemic gene therapy, where a second treatment would lead to a lack of effect due to neutralising antibodies. The most commonly used delivery route for ocular gene therapy is pars plana vitrectomy, followed by subretinal bleb formation and injection of the gene therapy product. Alternatively, gene therapy can be delivered by the supra-choroidal route, avoiding the need for vitrectomy.

Also, intravitreal administration of gene therapy is under development; while easiest to administer, it has the potential to infect a wider retinal area but comes with a slightly higher pan-ocular and potentially systemic exposure, which may induce inflammatory and immune responses. To avoid inflammation and immune responses, preventive corticosteroid regimens are used, and patients are very closely monitored during the first months after treatment. Furthermore, the follow-up durations in clinical trials are very long – five to 15 years – to detect any long-term safety issues and to monitor the sustainability of the trans-gene effect after the single treatment. It is therefore important to select the right patients, willing and able to comply with the burden of study protocols and study length. Particularly in retinal and neuroretinal diseases, patients with sufficient function preserved should be targeted, as the goal is to slow or halt the progression of the disease.

Medical and scientific considerations

While many gene therapies target rare diseases, which can be challenging for patient recruitment, these patients and their families are highly motivated. With often no treatment options available, patients are very eager and educated about upcoming trials and therapies. Working with advocacy groups keeps patients and their families updated on new technologies and innovations.

A challenge, particularly in rare ocular diseases, is to select outcome assessments that are clinically important, have sufficient potential to be improved given the mechanism of action of the treatment under study, are validated and are accepted by regulatory authorities. In rare diseases, with little or even no trial experience, this is not always possible, and endpoints may have to be validated within a clinical development plan following discussions with regulatory authorities. Imaging plays a significant role in ophthalmic R&D, offering many non-invasive evaluation methods of ocular structures. This allows for the assessment of preservation of eye structures effectively over time and quantifying changes after experimental treatments in clinical studies. Furthermore, many of these imaging or anatomical biomarkers are closely associated to functional vision outcomes, which is of ultimate importance to patients.

> *Many ophthalmology studies aim to treat rare diseases, which adds difficulty to identifying and enrolling patients with a specific indication*

There are also challenges regarding the methodologies of applying imaging outcome assessments in clinical trial settings, particularly when local imaging assessment is applied, likely introducing intra-patient and interpatient variability. Using a central reading centre is important in a clinical trial setting for rapid, reliable and reproducible image assessment.

Operational considerations

With the recent advances in ophthalmology drug development, the management of ophthalmology trials is becoming increasingly complex, and understanding common operational considerations is essential to execute a study successfully. First, ophthalmology sites often don't have all the necessary equipment for studies beyond common ophthalmology-specific equipment. The study team must assess sites for necessary equipment during the feasibility process. For example, sites may need specific equipment to capture required images, such as a microperimeter, -70° freezers for lab sample storage, protocol required visual acuity charts, etc. In those cases, the

clinical research organisation (CRO) will do an inventory and source sites with the necessary equipment to conduct the study successfully.

Next, it is recommended to select imaging modalities and ophthalmic exams that correlate strongly with functional outcomes, such as visual acuity and visual function, needed for activities in daily life. In pivotal phase 3 trials, an actual visual function test, such as a multi-luminance mobility test, where patients navigate through a maze of obstacles with varying luminance levels, may be the primary outcome assessment for efficacy of investigational treatment. Recently, virtual reality devices to test visual function became available, alleviating sites from a large and burdensome multi-luminance mobility lab while offering an easy-to-perform validated virtual reality mobility test. These had controlled learning effect, excellent reproducibility and high agreement between real and virtual conditions, as well as sensitivity and specificity to measure disease progression and therapeutic benefit in retinal dystrophies. An advantage of selecting correlating biomarkers and tests in this specific ophthalmic setting follows from the impossibility of doing visual function mobility testing in clinical practice because clinics do not have such large visual mobility testing labs. Therefore, the correlation with visual field testing, a surrogate endpoint for vision, allows for easy monitoring of treatment effect in daily practice, as this test is available everywhere. Visual acuity assessments can be affected by the subjectivity of the technicians administering the assessment, which can impact the assessment if not managed appropriately with adequate training. An outside vendor is typically required to certify the lane to ensure proper distance and equipment are available, and certify the technicians administering visual acuity assessments. One strategy to ensure consistency of results is to have the same technician conduct all assessments for an individual patient for the duration of the study. To help eliminate disparities, vendors typically provide sites with training documents to reference, creating standardisation and consistency across individual technicians and sites.

Finally, feasibility and recruitment support for rare ophthalmology trials add another level of operational consideration. Many ophthalmology studies aim to treat rare diseases, which adds difficulty to identifying and enrolling patients with a specific indication. Patients may not be located near sites and must travel far to participate in the study. It is important to ease the patient burden and provide resources to help them travel to a site. Investigating indication incidence rates can help find where patients may be pocketed and identify sites in those areas. 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 an internal genetic database of their patients, which is useful during feasibility.

Sites without prior gene therapy experience can screen eligible patients before sending them to central dosing sites with prior gene therapy experience. Once patients receive the intervention at the central dosing site, they can visit their local site without gene therapy experience for future follow-up appointments. Sponsors should be mindful of making travel accommodations for patients and their families to reduce patient burden further. To boost patient recruitment and retention, sponsors can lean on advocacy groups, ad campaigns and digital health technologies to increase awareness of ongoing trials. Healthcare providers and genetic counsellors can also help dispel patient concerns over gene therapy safety, a major enrolment barrier. While some patients might be sceptical of gene therapy trials with limited preclinical evidence, others are motivated to try a new therapy that could lead to a better life.

Regulatory considerations

When developing an innovative product, engaging early with the regulators is essential, especially for gene therapy products. The FDA recommends communication early in product development through an INTERACT or a pre-IND meeting. Special designations are also available, which confer benefits such as more intensive agency support and can potentially reduce time to approval. In the US, these procedures include RMAT designation for regenerative medicine therapies for serious or life-threatening diseases or

conditions, which is also applicable to many gene therapies, and Breakthrough Therapy designation, which is designed to expedite the development and review of drugs that are intended to treat a serious condition and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). In the EU, the PRIME procedure provides additional regulatory advice and incentives.

Furthermore, orphan drug designation is available in many countries, including the US and EU, which confers financial and regulatory benefits for products for rare diseases. All the expedited procedures have different criteria, benefits and acceptance rates, so the global regulatory strategy must be carefully considered to facilitate drug development and approval. If in-depth regulatory expertise is unavailable in-house, an experienced full-service CRO can support these activities. When starting up an ophthalmology study site, it is crucial to identify the correct personnel at the site level, including all sub-investigators who will participate. Additionally, it is essential to identify the process at each site early on, including IRB/IEC and IBC/GMO, as applicable, or any other ancillary committee reviews that need to occur. When developing an informed consent form (ICF), sponsors should ensure that it includes all necessary information. A CRO regulatory team can review the ICF to identify any missing elements the regulators may question and ensure it contains pertinent patient information, including details on study procedures. A detailed and accurate ICF helps facilitate a seamless trial process, ultimately leading to a faster approval process.

It is essential to have a regulatory team involved in a trial from the beginning because the team accumulates knowledge on site preferences and processes, benefitting future collaborations. Leveraging historical data and insights through a clinical trial management system eliminates the need to reinvent the wheel each time working with a site, ultimately reducing the burden on sites while streamlining the process for sponsors.

Conclusion

The field of ophthalmology holds immense promise for restoring vision and improving the lives of those with hereditary retinal diseases, and ongoing research and innovations continue to advance the field. Ophthalmology clinical trials require a CRO partner who understands the medical, operational and regulatory considerations to overcome complexities and accelerate the path to approval.

References

1. *Visit: citeline.com/en/products-services/clinical/pharmaprojects*
2. *Visit: fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss*

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