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Current Status of Clinical Trials Design and Outcomes in Retinal Gene Therapy

Boris Rosin,[1] Eyal Banin,[2] and Jose-Alain Sahel[1,2,3]

[1]The UPMC Vision Institute, University of Pittsburgh, Pittsburgh, Pennsylvania 15219, USA
[2]Division of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel
[3]Institut Hospitalo-Universitaire FOReSIGHT, Paris 75012, France

Correspondence: brosin@pitt.edu

With the rapid expansion of methods encompassed by the term gene therapy, new trials exploring the safety and efficacy of these methods are initiated more frequently. As a result, important questions arise pertaining the design of these trials and patient participation. One of the most important aspects of any clinical trial is the ability to measure the trial's outcome in a manner that will reflect the effect of the treatment and allow its quantification, whether the trial is aimed at preservation or restoration of retinal cells (photoreceptors and others), vision, or both. Here we will review the existing methods for quantification of trial outcomes, stressing the importance of assessing the participant's visual function and not just visual acuity. We will also describe the key considerations in trial design. Finally, as patient safety remains the primary concern in any trial participation, we will outline the key principles in that regard.

The FDA approval of voretigene neparvovec rzyl (AAV2-hRPE65v2), a subretinal injection of a viral vector for the treatment of Leber's congenital amaurosis (LCA) consecutive to mutations in the *RPE65* gene (LCA2; NCT00999609), ushered in a new era of gene therapy trials and, more broadly, vision/visual function restoration trials. With well over 250 known genes causing inherited retinal dystrophies (IRDs) (Pontikos et al. 2020), the potential for novel treatments using gene therapy opened a very large perspective. Gene-replacement techniques continue to evolve and improve. Adjustments to existing technique include methods to enhance mitochondrial function (Chadderton et al. 2023), employed in mitochondrial DNA mutations such as Leber's hereditary optic neuropathy (LHON) (Newman et al. 2021). Interestingly, such approaches need not be limited to gene therapy, as much simpler interventions (e.g., increasing the intraocular pressure as a means of induction of ocular stress) were shown to enhance the transfer of gene therapy for LHON (McGrady et al. 2023). However, gene therapy is by no means limited to the classic gene-replacement approach, exemplified by voretigene neparvovec rzyl, as the term encompasses many different techniques.

Gene-editing techniques, such as CRISPR-Cas9, have shown great initial promise in in vitro studies (Zhang et al. 2021) and are now being tested in clinical trials in human patients affect-

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ed by IRDs (NCT03872479). In a subtype of IRDs characterized by a gain-of-function mutation, gene replacement needs to be paired with gene-silencing techniques, some of which act at the RNA level and are designed to control/interfere with the expression of an aberrant protein causing the disorder (Orlans et al. 2021). Gene augmentation, the change of function of existing cells and genes to achieve a therapeutic goal, is another novel approach to gene therapy (Xi et al. 2022). While the approaches described above require surviving target cells, either photoreceptors or ganglion cells, for success, optogenetics, a novel gene therapy approach to the treatment of IRDs, can be used even in cases of widespread photoreceptor loss. The introduction of opsins into the surviving inner retinal cells by means of gene therapy in essence converts them into photoreceptors, with initial safety studies showing great promise (Sahel et al. 2021a) and clinical trials continuing (NCT03326336). Finally, employing gene therapy for introduction of trophic factors known to increase the survival of photoreceptors (e.g., rod-derived cone viability factor [RdCVF]) was shown to promote protection of photoreceptors in murine models of cone-rod dystrophy (Byrne et al. 2015), leading to ongoing phase Ib-IIa trials in patients (NCT05748873).

Unfortunately, far from all gene therapy trials culminate in success, as was the case with the first X-linked *RPGR* gene therapy trial (NCT03116113), despite showing promise in safety trials and some post hoc analyses (von Krusenstiern et al. 2023). Similarly, an RNA-based approach for the treatment of LCA10, while initially showing promise in safety trials (Russell et al. 2022), failed to reach the predefined end points in the subsequent phase 3 trial (NCT03913143). However, such "failures" may reflect flaws in the design of trials. Thus, the need for improving trial design as well as the methods for estimation of outcomes, such as vision/visual function and retinal structure, is self-evident.

The above is not meant to represent a comprehensive review of gene therapy approaches and trials, but rather to impress upon the reader the current scope of the field. This includes in particular the marked differences between the approaches encompassed by the term "gene therapy," as well as the variability of outcomes, even in treatments initially showing great promise. We have not even mentioned nongene therapy approaches, such as cell therapy and retinal prostheses, for instance.

METHODS FOR OUTCOME ESTIMATION

Visual Acuity and Contrast Sensitivity

While visual acuity is the main method for estimation of visual system function in the clinical setting, and it remains a main component of every attempt to estimate the outcomes of a therapeutic intervention, its usefulness in clinical trials for the treatment of IRDs is somewhat limited. In many of the patients considered for IRD treatment trials, visual acuity is rudimentary. Such is the case in LCA, where poor vision from birth is one of the defining features of the disorder described by Leber in 1869 (Leber 1869). In many cases, ascertaining poor visual acuity is an important parameter for patient inclusion in the study, as patients with preserved visual acuity could potentially lose some of that acuity in an unsuccessful trial. With gene-replacement attempts aimed toward preservation of remaining cells and not their restoration, one does not expect visual acuity to change significantly in a case of a successful intervention. Nevertheless, in trials targeting macular dystrophies and optic nerve disorders, visual acuity may provide compelling data.

Estimation of visual acuity could be performed by the classic ETDRS (Ferris et al. 1982) or the Bailey–Lovie letter charts (Bailey and Lovie 1976). Contrast sensitivity, classically measured by the Pelli–Robson charts (Pelli et al. 1988), could also be estimated by more novel technological approaches (Pelli and Bex 2013). Interestingly, studies have shown that contrast sensitivity (along with visual field) affects functional vision, as estimated by mobility performance, more significantly than visual acuity (Marron and Bailey 1982). In children and nonverbal adults, both visual acuity and contrast sensitivity could be estimated by objective measures employing vision-dependent reflexes, such as the optokinetic nystagmus (OKN) (Hyon et al. 2010), albeit the relationship between these

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parameters is complex (Çetinkaya et al. 2008). Of note, OKN responses are the main method for estimation of visual acuity in laboratory animals, and many commercial systems employing the OKN exist (Prusky et al. 2004).

In patients with low vision, the measurement of vison off-chart is less accurate and various attempts to provide reliable quantitative measurements have been put forth (see collections.lib.utah.edu/ark:/87278/s6768n5w) (Schulze-Bonsel et al. 2006; Karanjia et al. 2016).

An alternative approach used in estimation of functional vision in low-vision patients is the use of self-reporting questionnaires, which incorporate the patient's self-assessment of their performance of tasks of daily living. These include the Veterans Affairs Low-Vision Visual Functioning Questionnaire (Stelmack et al. 2004) and the National Eye Institute Visual Function Questionnaire (Mangione et al. 2001), among others. Patient-reported outcomes are becoming increasingly important in this respect (Lacy et al. 2021).

Advanced Psychophysics

Electrophysiology

Since its original description by Ragnar Granit in 1933 (Granit 1933), the full-field electroretinogram (FFERG) has been the mainstay of electrophysiological testing of retinal function in generalized retinal dystrophies. In a similar manner, since the almost simultaneous description of Adrian and Matthews in 1934 (Adrian and Matthews 1934), the visual-evoked potentials (VEPs) test has been used largely for the estimation of function of the visual pathways and during the pre–magnetic resonance imaging (MRI) era was in fact considered to be an important testing modality for the diagnosis of multiple sclerosis presenting with optic neuritis (Halliday et al. 1972). Notably, the VEP response is predominated by macular function and can thus serve as a measure of interventions aimed at the macula (Holder 2004). Multifocal ERG (MFERG) is another useful tool to estimate macular function and offer localization of retinal defects (Hoffmann et al. 2021). In pattern VEP, stimuli are used to correlate optic pathways function to visual acuity and checkered pattern VEP has been used to that aim for many years (Harter and White 1968; Regan 1973). Pattern ERG is another method (Riggs et al. 1964) employed for estimation of both retina and optic pathways function (Berninger et al. 1988). The International Society for Clinical Electrophysiology of Vision (ISCEV) defines standards for the reporting of electrophysiological recordings and their analysis (Hamilton et al. 2021; Robson et al. 2022).

Color Vision

Farnsworth hue testing (Kinnear and Sahraie 2002) and the Ishihara plates (Ishihara 1972) have been the mainstay of color vision testing and provide a good estimation of macular function and by extension of the optic nerve (Ménage et al. 1993), where the macular fibers have a much more prominent representation than the fibers originating in the peripheral retina (Holder 2004). Of these, the Farnsworth–Munsell D-15 is perhaps the most useful in the setting of IRDs, where it has been successfully used to estimate cone function (Okajima et al. 1982; Wissinger et al. 2008). This is especially true since the Ishihara and other color vision tests require significantly preserved levels of visual acuity, as opposed to the hue recognition–based tests (Ng and Shih 2017).

Dark Adaptation

Dark adaptation testing is another useful modality for the estimation of retinal function. In particular, the longer latency rod dark adaptation curve is useful in quantifying rod photoreceptor function (Roman et al. 2005), whereas the absence of the rod-cone break is a useful tool in the estimation of cone dysfunction in achromatopsia (Aboshiha et al. 2014), which has recently emerged as the target for gene therapy in several trials (NCT02935517, NCT02599922).

Visual Fields

Visual fields are progressively constricted in many of the IRDs, causing significant dysfunc-

tion and impacting the patients' quality of life (Sugawara et al. 2009). The use of the static Humphrey visual fields, the mainstay of clinical practice in the management of glaucoma, is limited in the evaluation and management of IRDs. However, the 10-2 field has been used in more advanced disease with only a central island of viable photoreceptors remaining (Sayo et al. 2017). Nevertheless, kinetic perimetry has traditionally been the modality of choice for the evaluation of visual fields in IRD patients (Berson et al. 1985). In the past two decades, the classic Goldmann kinetic visual field test has been gradually replaced by the Octopus semiautomatic kinetic visual field, and studies have found the two testing modalities to be comparable (Barnes et al. 2019). Recently, the static GATE (German adaptive threshold estimation) protocol has been used more frequently in the evaluation of visual fields of patients participating in clinical trials (Schiefer et al. 2009; Buckley et al. 2022). In addition, microperimetry, somewhat better termed fundus-controlled perimetry, is slowly gaining a very central role in the management of patients of IRDs. In this testing modality, the stimuli are projected directly onto the retina with retinal image registration, allowing to control for patients' eye movements, and the test provides a localized measure of retinal sensitivity mapping (Bagdonaite-Bejarano et al. 2019). As such, this approach allows to map out the preferential retinal locus (PRL) of each individual patient (Schönbach et al. 2022), which is of utmost importance for clinical trials aimed at preservation of the remaining photoreceptors (Yang and Dunbar 2021) as well as the planning of interventions better served by avoiding the PRL, such as in retinal prostheses implantation (Palanker et al. 2022).

Imaging in Relation to Psychophysics

Fundus autofluorecense (FAF) has been demonstrated to be a useful adjunct in the estimation of retinal function, as an abnormal fluorescence area in FAF negatively correlates with the extent of the patients' visual field (Oishi et al. 2013). With the considerable advancements of ocular coherence tomography (OCT) technologies, the OCT analysis of IRD patients has taken the leap beyond the mere volumetric changes, which still provide significant amounts of useful information (Oh et al. 2020). OCT angiography is used to demonstrate angiographic changes in IRD patients (Cabral et al. 2020) and even monitor progression (Jauregui et al. 2018). Furthermore, due to the high resolution of imaging achieved by OCT, techniques to image the substructures of the photoreceptors have proven to be useful in ascertaining their viability. Thus, in an ongoing study, a specialized algorithm looking at OCTs of patients with generalized IRDs demonstrated a substantial subpopulation of such patients with a measurable volume of alive but dormant cone photoreceptors, making them perhaps amenable to gene therapy and other preservation therapy approaches (Janeschitz-Kriegl et al. 2022). In addition, capitalizing on the ability of the newer OCT devices to demonstrate changes on the micrometer scale, such changes were demonstrated to occur in the initial phase of phototransduction and were found to be repeatable and quantifiable. This, in essence, introduced a new discipline bridging imaging and psychophysics, termed optoretinography (Pandiyan et al. 2020). Potential implications are profound, as one can envision incorporating functional testing into the standard OCT testing performed for many of the patients seen in a retinal clinic. Adaptive optics, an imaging technique allowing in essence resolution on the level of a single cell, in itself an important imaging modality in assessing photoreceptor health (Salmon et al. 2017), further adds to the capability of optoretinography (Cooper et al. 2020).

Visual Function versus Functional Vision

Introduction

The difference between visual acuity, defined as the ability to discern optoptypes at a given distance, and visual function, defined as the ability to perform a vision-dependent task, is well established. For instance, it has long been known that visual acuity in patients with advanced age-relat-

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ed macular degeneration does not predict the ability to recognize certain objects and faces, given the same contrast sensitivity levels (Alexander et al. 1988). In the recent preliminary results of IRD treatment by means of optogenetics, an algae-derived opsin, ChrimsonR, was introduced into the surviving cells of the inner retina of a subject with advanced retinitis pigmentosa (RP) and light perception (LP) vision. Following treatment, he was able to detect objects when using the specialized goggles required for the activation of ChrimsonR, while his visual acuity remained LP, in a clear separation between visual acuity and function (Sahel et al. 2021a). On the other hand, patients with RP and visual field constriction, reported a significant functional impairment using the vision-related quality of life questionnaire, despite having relatively preserved visual acuity (Lange et al. 2021). Thus, the importance of developing methods to estimate visual function independently of visual acuity is paramount. To that means, the FDA has put forth guidelines, the Investigational Device Exemption (IDE) Guidance for Retinal Prostheses, describing the essential requirements for any test aimed toward quantifying visual function in trials evaluating retinal prosthetic devices (www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemption-ide-guidance-retinal-prostheses).

Object Recognition

As described above, object recognition has recently been shown as a useful method of visual function estimation (Sahel et al. 2021a). Similar approaches include picture discrimination tests (Gulati et al. 2011) and tools designed to assess instrumental activities of daily living in low vision patients (Finger et al. 2014). While these may seem as rudimentary levels of visual function, especially compared to these of patients with measureable visual acuity, the impact on patient's lives can be dramatic. Furthermore, while IRDs are relatively rare, these disorders represent a frequent cause of blindness in both children and young adults, whereas blindness in these age groups is considered to be one of the major socioeconomic burdens on medical-related expenditures in the developed world (Frick et al. 2007, 2010).

Navigation Tasks

Introduction

When examining the components of disability of patients with retinal dystrophies, one of the most frequently reported issues is the inability to navigate in unfamiliar environments (Prem Senthil et al. 2017). Thus, navigation tasks have quickly become the preferred method for estimation of visual function in IRD patients.

The MLMT

The multiluminance mobility test (MLMT) (see Chung et al. 2023) was the functional test used during the trials leading to the FDA approval of voretigene neparvovec rzyl (Chung et al. 2018). In this test, the subject performs a navigational task upon a relatively small (7×12 feet) canvas divided into squares. The desired path is denoted by arrows of sufficient size to allow visualization by an individual with a visual acuity of 20/200. Obstacles are introduced in squares both within and outside of the desired path, either conceptually (e.g., black squares representing holes) or physically (e.g., elevated squares within the path). A randomized path is created before each trial. The speed of completion as well as accuracy are scored and combined into a single score.

The importance of the MLMT is undoubtedly in the introduction of a standardized method to assess patient mobility. However, its design had some significant drawbacks. First and foremost, the limited navigation space required patients to adjust their navigation speed to the constricted environment. Furthermore, the composition of the score, reliant only on speed and accuracy of completion and offering strict discretization (lowest score of -1 to highest score of 6), did not adequately reflect the intrinsic complexities of the mobility challenges experienced by patients with IRDs. Finally, the use of conceptual rather than real obstacles created an unrealistic environment poorly representative of day-to-day navigational tasks.

The Streetlab

The Streetlab is an indoor simulation environment designed to mimic the complexities of a real urban street. Its large size (30 × 23 feet) is further enhanced by images projected on the walls of the setup (Fig. 1). Real-time obstacles (e.g., plants, garbage bins, stepladder) are introduced. A sound system is used to introduce real street sounds into the environment.

Multiple parameters are recorded and analyzed. In addition to the accuracy and time to completion, as measured by the MLMT, time to motion initiation after the "go" signal, time to walk 12 feet in a straight line without obstacles, and other similar parameters are recorded. Furthermore, the subjects' motion is recorded by a closed-loop video system and their gait is analyzed to include, in addition to their trajectory, the number of turns and collisions. The tasks are performed under different illumination conditions (Sahel et al. 2021b).

In addition to providing the means to create a controlled environment for visual function testing, the Streetlab offers several advantages over the MLMT. First, it creates a realistic environment of a real-life situation, such as navigating an unfamiliar street, a situation which IRD patients consistently report as one of the most challenging aspects of their visual disability (Sugawara et al. 2009). Furthermore, it offers a multitude of parameters for the quantification of the changes in visual function, adequately representing the intricacies of all the aspects of a successful navigational task. Finally, the use of highly flexible and adaptable environment, allows the utilization of the individual patient's "coping mechanisms" (i.e., the strategies they adapt to improve their visual function) (Authié et al. 2017; Sahel et al. 2021b).

Virtual Reality Constructs

With the use of augmented and virtual reality gaining a more central place in our lives, the use of virtual reality constructs is an intuitive approach to creation of custom navigational tasks for visual function estimation. To date, no uniform approach to the design of such tasks exists

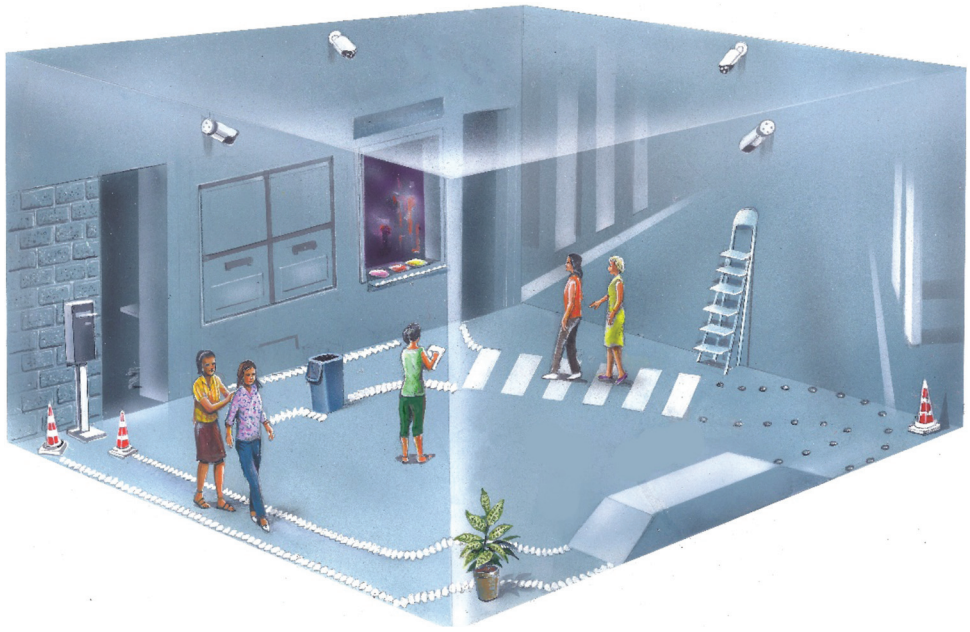

Figure 1. A schematic representation of the Streetlab. Each patient is accompanied by a mobility specialist. A central coordinator is monitoring their performance and taking notes. Video recording is stored for offline analysis of gait and movement initiation. (Illustration provided by Tuvia Kurtz.)

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and standardization is required to incorporate such tests as acceptable outcome measures in both observational and interventional trials (Authié et al. 2023; Pur et al. 2023).

Considerations in the Design of Clinical Trials

Introduction

With IRDs presenting a significant cause of visual disability worldwide (Cross et al. 2022), standardization of performing clinical trials is of the utmost importance. The Second Monaciano Symposium for the Advancement of Clinical Trials for IRFDs set forth recommendations for the performance of such trials (Thompson et al. 2020). While a comprehensive discussion regarding such strategies is beyond the scope of this review, we will mention here what we believe to be the most pivotal points when designing a study aimed at furthering the understanding and developing treatments of IRDs.

Observational Studies

These should ideally be performed prior to the interventional study, with the aim to adequately describe the natural history of a genetic condition. Naturally, for any study aimed at furthering the understanding of or developing a new treatment modality for IRDs, a precise genetic diagnosis of the condition is crucial. This will not only exclude nongenetic cases, but could also provide information about the significance of different mutations in disease phenotype. Notably, phenotypes tend to express variation even for the same mutation in different patients.

Ideally, an observational study should collect as much clinical information as possible regarding the IRD in question. Practically, and as shown in this review, the large amount of different testing modalities makes it impossible to perform all for each study. Out of the modalities listed above, visual acuity, contrast sensitivity, color vision, visual fields, basic imaging (fundus photos, FAF, and OCT) and a baseline FFERG are essential. The latter is also useful as an end point test, provided the baseline ERG is recordable. Additional testing modalities should be adapted to fit the disease in question (e.g., MFERG for maculopathies vs. dark adaptation for achromatopsia). Visual function tests are very useful to quantify the resultant disability.

Interventional Studies

Perhaps the most important aspect of an interventional study is the selection of an appropriate outcome measure. Many times, no single appropriate testing modality will exist, and multiple modalities or even custom-developed testing modalities will have to be used as the outcome measures. Custom modalities will need to be standardized and validated. As shown above, functional tests are of the utmost importance for any interventional study, as they cannot only ensure benefit but also guard against possible harm.

Among the key questions to address while designing a trial are the following

- Is the expected outcome vision restoration or solely preservation? What are the patient's expectations?
- Are solid, reliable natural history data available to refine outcome measures?
- What are ways to cope with the natural variability of structural and functional parameters?
- Is efficacy better demonstrated using structural versus functional changes, or both, and over what time period?

Ethical considerations are of utmost importance for any interventional trial. We need to ensure that the patient receives all the information about the intended treatment in accessible language and is allowed enough time to reach an informed decision about participation. *Primum non nocere* should continue to be the main guiding principle for all interventions. We should strive to ensure that patients of any socioeconomic status would be able to benefit from a novel treatment in an equal manner. Finally, with a multitude of information available online, we should be prepared to provide guidance to patients seeking our advice regarding a planned trial offering them participation.

SUMMARY

As we enter a new and exciting era of a multitude of therapies and approaches being either developed or, in some cases, already available for IRDs, we should strive to continue to improve all aspects of clinical trials. Where possible, standardization of outcome measures should be employed. Testing modalities should be tailored to the individual patient, aiming to not only to allow better quantification of interventional outcomes, but also to ease the patient's clinical burden associated with trial participation.

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Boris Rosin, Eyal Banin and Jose-Alain Sahel

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