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Review

Advancing Clinical Trials for Inherited Retinal Diseases: Recommendations from the Second Monaciano Symposium

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Major advances in the study of inherited retinal diseases (IRDs) have placed efforts to develop treatments for these blinding conditions at the forefront of the emerging field of precision medicine. As a result, the growth of clinical trials for IRDs has increased rapidly over the past decade and is expected to further accelerate as more therapeutic possibilities emerge and qualified participants are identified. Although guided by established principles, these specialized trials, requiring analysis of novel outcome measures and endpoints in small patient populations, present multiple challenges relative to study design and ethical considerations. This position paper reviews recent accomplishments

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and existing challenges in clinical trials for IRDs and presents a set of recommendations aimed at rapidly advancing future progress. The goal is to stimulate discussions among researchers, funding agencies, industry, and policy makers that will further the design, conduct, and analysis of clinical trials needed to accelerate the approval of effective treatments for IRDs, while promoting advocacy and ensuring patient safety.

Introduction

Building on over a century of ophthalmic and basic research, remarkable progress is being made in the rational design and clinical testing of potential therapies for inherited retinal diseases (IRDs). New understanding of the genetics and biology of the retina, along with technical advances and improved outcome measures, have opened the way for human trials of innovative forms of therapy, including small molecules, DNA and RNA therapies, microelectrode arrays, and cell transplantation. As of this writing, over 50 interventional studies for IRDs are listed as active in the US National Clinical Trials Database,[1] reflecting record high levels of patient participation and expectations. At the same time, the significant costs relative to the small target population, and the involvement of multiple corporate and private stakeholders, have created a landscape filled with complex challenges.

To better understand the concerns of this rapidly evolving field, an international group of retinal dystrophy experts established the Monaciano Consortium, whose first meeting was held in 2013. The result was a set of recommendations addressing existing gaps relative to diagnostics, natural history studies, interventional study design, and outcomes analysis.[2] Since that time, researchers in the field have acted on many of these recommendations, particularly those focused on advancing the development of clinical trials. A comprehensive overview of the current IRD landscape, as well as remaining knowledge gaps was recently published.[3]

The Monaciano Consortium convened a second symposium in October 2018 focused on reaching a consensus view of the priorities that should guide the next phase of research and development in IRD clinical trials in the next 5 to 10 years. As a result of discussions at the meeting, seven priorities were identified: (1) using natural history studies to guide clinical trial design; (2) developing outcome measures meaningful to patients; (3) standardizing validated outcome measures; (4) reducing inflammation associated with IRDs and gene therapy; (5) developing a pediatric action plan; (6) improving advice to patients; and (7) promoting transparency, accountability, and accessibility.

The present article reviews the current status and unmet needs of clinical trials for IRDs and provides a detailed set of recommendations for advancing progress in priority areas viewed as critical for accelerating the development of effective therapies for these blinding diseases.

The Genetic Landscape

Since the discovery of the first retinal disease gene over 30 years ago,[4] more than 270 different genes responsible for hereditary retinal diseases have been characterized, and others have been mapped and

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remain to be identified.[5,6] Retinitis pigmentosa (RP), the most common IRD, has an estimated prevalence of 1 per 3500, and affects over 2 million individuals worldwide, with mutations in any 1 gene exhibiting widely varying prevalence.[7] As a result of major advances in sequencing technology and data sharing, genetic testing for mutations in IRD genes is now a mature clinical science. Strategies for increasing the efficiency of IRD genetic testing include the use of disease-related gene panels, retinal targeted-capture next-generation sequencing (NGS), whole-exome and whole-genome NGS, long-read sequencing, haplotype assembly, and linkage mapping.[8–14] Together these methods provide an average mutation identification yield of 60% to 80%, and even higher, depending on the disease, testing paradigm, and population under study.[15]

There is increasing recognition of the importance of ascertaining the genetic cause of IRD for all participants in clinical trials, whether or not interventions are gene-specific.[16,17] Defining genetic etiology is fundamental for excluding individuals with retinal disease not caused by genetic factors, and for establishing the prognosis, risk to other family members, and relevance of potential therapies.[18,19] Currently, nearly half of individuals tested do not receive a genetic diagnosis,[20,21] and many others do not have access to genetic testing, receiving only a descriptive diagnosis that is associated with mutations in a number of different genes or inheritance patterns.[22–24] However, the reality of achieving a genetic diagnosis for all affected individuals appears to be within reach, as mutations in the currently known IRD genes are estimated to account for the disease in approximately 90% of affected individuals.[25] In addition, significant progress is being made in solving variants of unknown significance, consistently detecting intronic and structural variants, and increasing access to genetic counseling and curated databases. Furthermore, decreased costs and technical improvements in whole-genome sequencing, including the use of field-deployed instruments, is expected to dramatically increase the potential of genetic diagnostics outside of traditional patient-provider relationships.[26,27]

These advances are predicted to expand the scope of genetic testing beyond the extensively studied populations in Europe and North America to those in Africa and large areas of Asia where access has been limited. Massive increases in patient-centered data sharing are expected to result from the growth of global open databases, such as ClinVar and the Leiden Open Variation Database.[28,29] The inclusion of both genetic and standardized phenotypic information is expected to improve the interpretation of genetic variants and associated diagnoses, and to support efforts to replace historical names for IRDs with standardized nomenclature that provides genetic context for guiding treatment decisions. Together, these advances will be fundamental for continuing the movement of the IRD field toward the practice of precision medicine, which considers individual variability to better predict efficacy in different groups of people.[30]

The Clinical Trials Landscape

The recent explosion of genetic information and therapeutic approaches, including the first gene therapy approved by the US Food and Drug Administration (FDA),[31] have resulted in a rapid increase in IRD clinical trials and natural history studies. Phase 1/2 trials have been initiated for gene augmentation for recessive loss of function; gene knockdown and replacement for dominant disease; delivery of targeted drugs, including visual cycle inhibitors, retinal chromophores, and complement inhibitors; oligonucleotide therapy for RNA modulation; small molecule therapy for readthrough of premature stop codons; and most recently recruiting genome editing using CRISPR/Cas9.[1,32] In addition, trials using stem cell–derived retinal pigment epithelium (RPE) have been initiated for Stargardt disease (STGD) and RP, and trials using retinal progenitor cells for RP and macular degeneration have been initiated or completed.[33–38]

As clinical trial activity rises to new levels, the field appears poised to make rapid and important advances in IRD research and patient care. Nevertheless, clinical trials are lengthy and highly experimental undertakings, which rely on doctor-patient interactions that exceed routine service provision, and which occur within a medical enterprise that provides little direct support. Most trials are financed by industry owing to their high cost, with FDA approval of a new drug associated with a median cost of $19 million in 2018.[39] Thus there is an urgent need to develop mechanisms and best practices that ensure a fair and mutually beneficial balance between corporate interests and those of patients and society. In addition, as the demand for resources intensifies, there will be increased pressure to prioritize trials on the basis of compelling disease pathology and basic principles that favor rapid outcomes and analysis, and to safeguard the resources needed for future trials in these small patient populations.

Although enthusiasm for gene-specific therapies remains high, this approach is limited by the time, effort, and funding needed to develop treatments for relatively small numbers of affected individuals. Mutation-independent approaches targeting shared pathogenic mechanisms at early stages of disease, or

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using regenerative therapies to replace photoreceptors at later stages of disease, are important alternative strategies for developing therapies for larger segments of the IRD population.[40–42] Efforts to elicit neuroprotection by targeting shared pathogenic mechanisms include the use of small molecules; restorative therapies include cell transplantation, genetic reprogramming, and optogenetics.[43]

Evaluating the potential usefulness of novel therapeutic strategies involves assessing specific outcomes using the most informative disease models available. Proof-of-concept gene-therapy studies have been performed in multiple species, including spontaneously occurring and genetically engineered laboratory, companion, and domestic animals, as well as nonhuman primates (NHPs).[44–47] Only a few NHP models of IRD are currently known,[47–50] however, their availability is expected to increase as a result of whole-exome sequencing efforts aimed at identifying natural variants, and the use of gene editing to generate engineered variants. Spontaneously occurring canine models of IRD represent another important resource,[51] as the similar sizes of canine and human eyes enable similar surgical approaches, immune responses are relatively similar to human, and the canine retina exhibits similar regional differences, including a cone-rich fovea-like area.[52] Twenty-six canine models have been identified to date, with gene-therapy studies performed in models of Leber congenital amaurosis 2, autosomal-recessive RP, autosomal-dominant RP, X-linked RP, cone-rod dystrophy, achromatopsia, and macular dystrophy.[51,53–55]

Key model systems include the use of patient-derived-induced pluripotent stem cells (iPSCs) to generate cultured RPE and retinal organoids for in vitro studies of human disease. Although still at an early stage of development, these platforms are already showing promise for elucidating pathophysiologic pathways in the context of human cell biology,[56] and are expected to play an increasingly important role in developing new therapeutic approaches for IRDs.[57,58] Comparative studies of therapeutic outcomes in iPSC-derived retinal cells with those in animal models will be key for determining the best uses of iPSC platforms for advancing progress in IRD precision medicine.

Outcome Measures and Endpoints

The genetic heterogeneity of IRDs, as well as diverse associated phenotypes, pose significant challenges to understanding disease pathology, predicting treatment benefit, and selecting outcome measures and endpoints for clinical trials. Of critical concern is the choice of metrics used to define treatment benefit, as acute improvements in visual function may not be achieved for some diseases. Instead, therapeutic effect may serve to delay disease progression and the time course of vision loss associated with a given disease.

The unique methodologies of vision testing and imaging have been used to develop multiple categories of outcome measures. For use as endpoints in clinical trials, outcome measures should be easy to obtain, highly repeatable and reproducible with minimal measurement or ascertainment error, possible to observe independent of treatment assignment, clinically relevant, and chosen before the start of data collection.[59] A well-defined primary endpoint is relied on to evaluate treatment safety or efficacy; numerous secondary endpoints are also usually evaluated, as these increase the chance of corroborating the presence or absence of the treatment effect, as well as safety.

A clinically meaningful endpoint is used to determine whether an intervention being studied exhibits substantial evidence of efficacy.[60,61] Clinically meaningful endpoints acceptable to the FDA and European Medicines Agency (EMA) and used in IRD clinical trials[62] include the mean change or mean rate of change in 1) best corrected distance visual acuity[63]; 2) visual field sensitivity (including analysis of hill of vision volumes)[64–66]; 3) retinal sensitivity measured by full-field stimulus testing (FST) [67]; and 4) multiluminance mobility tests (discussed later). A surrogate endpoint[60] is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict a clinically meaningful benefit.[61] Surrogate endpoints used in IRD clinical trials include the mean change or mean rate of change in 1) electrophysiological measures of retinal function[68]; 2) optical coherence tomography (OCT) documenting the rate of photoreceptor loss[69–71]; and 3) hypo- or hyperfluorescent lesion size on fundus autofluorescence.[72] Table 1 lists the outcome measures evaluated for the most commonly targeted IRD genes in clinical trials listed in Table 2. These outcome measures are quantified as the number of events, the change in the measure, or the rate of change.

Although measures of visual acuity, visual fields, and retinal structure are important, they do not convey other valued aspects of vision, including light sensitivity, dark adaptation, contrast sensitivity, and navigation. There is an urgent need to identify endpoint outcomes that reflect real-life challenges, and that can be assessed in subjects with differing ages and visual, cognitive, attentive, and physical abilities. In addition, endpoints are needed that reflect the dual aspects of central visual performance: visual acuity

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Table 1. Functional and Imaging Outcome Measures in Clinical Trials for IRDs in Table 2, as Documented at www.clinicaltrials.gov

		Disease Gene							
Outcome	Representative Tests	ABCA4	CEP290	CNGA3	CNGB3	REP1	RPE65	RPGR	RS1
Autofluorescence	FAF	X				X		X	
Color vision	Farnsworth D-15		X	X	X	X	X		
Contrast sensitivity	Pelli-Robson; quick CSF		X			X			
Gaze tracking	Position, stability		X						
Lesion size	FAF	X							
Light aversion	Light discomfort testing			X	X				
Macular sensitivity	Microperimetry	X	X	X		X	X	X	
Mobility assessment	Mobility performance; multiluminance mobility tests		X				X		
Patient reported visual outcome	Questionnaires: VFQ-25; Cardiff Visual Ability	X	X	X		X	X		
Pupillary response	Pupillometry		X				X		
Quality of life	Questionnaire		X	X	X		X	X	
Reading	Speed; Precision	X				X			
Retinal function	ERG, FST	X	X	X	X		X		X
Retinal structure	OCT	X	X			X		X	X
Retinal imaging	Fundus examination/photography	X	X	X				X	
Retinal vasculature	Fluorescein angiography	X		X					
Visual acuity	BCVA	X	X	X	X	X	X	X	X
Visual field	Perimetry, hill of vision	X	X	X			X	X	

BCVA, best corrected visual acuity; CSF, contrast sensitivity function; ERG, electroretinogram; FAF, fundus autofluorescence; VFQ-25, Visual Function Questionnaire-25 item.

that reflects the limits of distinguishing fine details at maximal black on white contrast, and contrast sensitivity that reflects the limits of distinguishing faint grayscale differences. Contrast sensitivity has been used as a key outcome measure in strabismus and amblyopia.[73–75] Patients with IRDs can experience deterioration of visual function and significant deficits in contrast sensitivity, even with relative preservation of visual acuity.[76] Strategies for evaluating rod function specifically, for example using two-color perimetry, are needed to develop sensitive measures that enable earlier detection of disease progression. Strategies for distinguishing rod from cone function, and quantitating cone function, are needed to assess outcomes in primary cone IRDs, including achromatopsia and blue-cone monochromacy.[77–79]

Imaging Endpoints

Powerful innovations in imaging are making important contributions to the characterization of IRD clinical phenotypes. Ongoing comparative studies of high-resolution imaging combined with other accepted modalities are expected to result in increased acceptance of imaging to document disease-specific changes in retinal features that are well-suited for use as surrogate clinical trial endpoints.[80–87] Important innovations involve the use of rapid image acquisition systems that reduce motion artifact, and advanced technologies for image interpretation, including artificial intelligence and machine learning. For example, analysis of retinal structure and visual function data aided by artificial intelligence are being used to determine localized treatment potential for IRDs.[88] Spectral-domain OCT is being used to generate high-resolution cross-sectional images of in vivo retinal structure, with applications to evaluating therapeutic outcomes in RP and STGD.[69,89,90] Imaging fundus autofluorescence, measured as near-infrared autofluorescence and/or as short-wavelength autofluorescence, is being used to describe the leading disease front[91] and evaluate therapeutic outcomes in STGD.[72,92] Adaptive optics

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Table 2. Multiple Interventions Targeting the Same IRDs in Ongoing and Planned Clinical Trials

IRD	Intervention	Study Sponsor	CT.gov identifier
***ABCA4*-related retinopathy**			
Gene therapy	EIAV-CMVp-ABCA4 (SAR422459)	Sanofi	NCT01367444
Visual cycle modulators	Emixustat (RPE65 inhibitor)	Acucela	NCT03772665
Complement factor inhibitor	ALK-001 (deuterated vitamin A)	Alkeus Pharmaceuticals	NCT02402660
hES-Derived RPE transplantation	Zimura (avacincaptad pegol)	IVERIC Bio	NCT03364153
	MA09-hRPE	Astellas Pharma	NCT01345006
***CEP290*-related retinopathy**			
Splice-modulating oligonucleotide	sepofarsen (QR-110)	ProQR Therapeutics NV	NCT03913143
CRISPR-Cas9 gene editing	EDIT-101 (AGN-151587)	Editas Medicine/Allergan	NCT03872479
***REP1* choroideremia**			
Gene therapy	AAV2-hCHM	Spark Therapeutics	NCT02341807
	AAV2-REP1	Nightstar Therapeutics/Biogen	NCT03496012
	rAAV2.REP1	STZ eyetrial	NCT02671539
	AAV-REP1	University of Oxford	NCT02407678
	4D-110	4D Molecular	Not available
***CNGA3* achromatopsia**			
Gene therapy	rAAV2tYF-PR1.7-hCNGA3	Applied Genetic Technologies Corp	NCT02935517
	AAV2/8-hG1.7p.coCNGA3	MeiraGTx	NCT03758404
	rAAV.hCNGA3	STZ eyetrial	NCT02610582
***CNGB3* achromatopsia**			
Gene therapy	rAAV2tYF-PR1.7-hCNGB3	Applied Genetic Technologies Corp	NCT02599922
	rAAV2/8-hCARp.hCNGB3	MeiraGTx	NCT03001310
***RPE65*-related retinopathy**			
Gene therapy	rAAV2/5-OPTIRPE65	MeiraGTx	NCT02946879
	rAAV2-CBSB-hRPE65	University of Pennsylvania	NCT00481546
	rAAV2-CB-hRPE65	Applied Genetic Technologies Corp	NCT00749957
	rAAV2/4.hRPE65	Nantes University Hospital	NCT01496040
	rAAV2-hRPE65	Hadassah Medical Organization	NCT00821340
	AAV2-hRPE65v2/Luxturna	Spark Therapeutics	NCT00999609; Approved
***RPGR*-related retinopathy**			
Gene therapy	rAAV2tYF-GRK1-RPGR	Applied Genetic Technologies Corp	NCT03316560
	rAAV5-hRKp.RPGR	MeiraGTx	NCT03252847
	rAAV8-RPGR (BIIB112)	Nightstar Therapeutics/Biogen	NCT03116113
***RS1* X-linked retinoschisis**			
Gene therapy	rAAV2tYF-CB-hRS1	Applied Genetic Technologies Corp	NCT02416622
	AAV8-scRS/IRBPhRS	National Eye Institute (NIH)	NCT02317887

scanning laser ophthalmoscopy, that removes optical aberrations from retinal images to generate high-resolution images of photoreceptors with single cell resolution,[93] is being used to monitor cones before significant loss of vision.[94–97] The discovery of so-called "dysflective cones" that appear to remain wired to native visual pathways[98–100] suggests that photoreceptors potentially amenable to rescue persist in the

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foveae in some IRDs beyond the stage of their loss of function.

Performance-Based Endpoints

Mobility course performance is being used to assess functional vision in a fixed environment. Mobility endpoints were used to establish efficacy for FDA approval of retinal array implants,[101] and further developed and validated for use in establishing FDA and EMA approval of gene therapy for mutations in *RPE65*.[102–105] A virtual platform for mobility testing has been developed that simulates an urban environment and incorporates integrated measurement tools permitting the evaluation of both vision and behavior.[106] This platform is also being used to assess the potential of changes in gait and gaze as novel clinical endpoints.[107,108] Although mobility testing requires substantial resources, continued development and validation efforts are expected to increase its importance in assessing therapeutic outcomes, especially for diseases with profound visual impairment.

There is also increasing recognition of the value of using performance-based tests (PBTs) and patient-reported outcomes (PROs) to establish endpoints for clinical trials. Survey instruments evaluating PROs that address issues of mobility, activity limitation, or health concerns have been developed for RP, congenital stationary night blindness, and STGD,[109] and instruments evaluating PROs that assess visual function and performance are also in use.[110–115] However, most existing PROs lack validation for application to specific IRDs, few PROs are relevant to individuals undergoing vision restoration therapies, and some PROs developed specifically for IRDs are proprietary and remain undisclosed.[109] Thus there is an urgent need to develop and validate additional IRD-specific PROs as outcome measures for use as clinical trial endpoints using FDA-recommended methods.[116–118]

Clinical Trial Design

Although the mechanics of phase 1/2 unilateral administration studies are well established,[119,120] the conduct of interventional clinical trials is a long, challenging, and expensive process that usually takes years. Cost is a main barrier, and thus most IRD clinical trials currently depend on partnership with industry. Decisions about which diseases and technology to pursue are often driven by business concerns, such as return on investment, that favor relatively prevalent diseases, intellectual property rights, and use of established technologies.

A fundamental aspect of clinical trial design is the choice of outcome measures that are tuned to the genetics, disease stage, and predicted effect (e.g., preservation vs. restoration), and that are appropriate for the patient population under study. This population increasingly includes children. Guidelines for demonstrating efficacy that are acceptable to regulatory bodies involve the use of outcomes measures that are clinically meaningful, validated, reliable, and sensitive to change.[59,120] In some cases, this requires developing new or improved outcome measures.[104] Multiple outcome measures are typically assessed, with the most clinically relevant outcomes used to determine safety and efficacy.

A key challenge in the design of IRD clinical trials is overcoming the limitations posed by the relatively small numbers of individuals available to participate. Strategies include the use of statistical methods applicable to small samples, including continual reassessment methods for phase 1 trials,[121,122] and dose-response modeling[123] and adaptive designs[124] for phase 2 and 3 trials, with consideration of the limitations of these approaches.[125,126] Additional challenges are posed by the extreme genetic heterogeneity of IRDs resulting in phenotypic diversity and variable disease progression. International natural history studies (e.g., the MacTel project[127] and the ProgStar study[128]) are used to predict the ages at which relatively rapid changes in disease progression are likely to occur, potentially identifying critical periods for therapeutic intervention and obtaining proof of therapeutic efficacy. This serves a similar purpose to the longitudinal cohort studies recommended in precision medicine,[30] and provides a powerful platform for decision-making regarding the inclusion of individuals in trials, the optimal mode of intervention, and the most informative outcome measures.

The increasing numbers of well-designed, yet complex, clinical trials have created an urgent need to enhance staffing at participating centers, and to increase international training of IRD specialists who will be needed as therapies become available worldwide. The logistical requirements of conducting these trials are enormous, with unmet needs for staff and expertise currently limiting the number of centers positioned to conduct trials. Strategies to meet these needs include collaboration and team approaches, and raise fundamental questions about who should be able to treat individuals with IRDs, for which there are currently no guidelines.

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Ethics, Advocacy, and Safety

As clinical trial activity for IRDs rises to new levels, it is increasingly important to foster and define realistic expectations for patients and providers. There is a critical need to provide guidance to individuals and their families about potential involvement in approved clinical trials, as well as their personal use of nonregulated therapies. The overarching ethical principles governing clinical trials are well established and are built on four pillars: 1) autonomy—requiring the decision-making process to be free from coercion or coaxing; 2) nonmaleficence—the mandate to "do no harm"; 3) beneficence—procedures must be done with the intent to benefit the patient; and 4) justice—all groups equally benefit or bear the burden of new or experimental treatments.

Advising individuals with IRDs about opportunities to participate in clinical trials is guided by standardized tools and protocols. The most important of these is the informed consent process that is conducted in accordance with the background, experience, and language of the individual. Individuals should be made aware of how to access information about trials for which they might qualify, including the risk-to-benefit ratio. Issues relevant to determining potential eligibility, inclusion and exclusion criteria, time commitment, travel considerations, and patient expectations should be addressed. Critically, areas for which there is a lack of knowledge should be acknowledged, unfounded bias toward specific trials should be avoided, and conflicts of interest should be disclosed. Strategies for dealing with conflicts of interest include obtaining a second opinion or ethics consultation, and learning from experts in other fields facing similar issues.[129–131]

These principles are particularly relevant when multiple clinical trials for a single IRD are testing the same or different categories of treatments, or when clinical trials are testing new treatments that promise better efficacy in diseases for which there are approved therapies. Ongoing and planned clinical trials testing multiple treatments targeting the same IRDs are shown in Table 2. Inclusion and exclusion criteria may dictate the choice in some instances, but not in others. For example, multiple clinical trials of AAV-RPE65 gene therapy have very similar inclusion criteria, and this is also the case for trials of AAV-RPGR gene therapy. When inclusion criteria are similar, there are no standardized guidelines to help physicians and patients decide in which trial to participate, or to assess the risks and benefits of an approved treatment relative to one that is potentially better, but still in clinical trials. In many cases, the choice to participate in a given trial comes down to informed consent, a process requiring more time for discussions than can be accommodated in routine clinics, and posing a significant burden for centers of excellence, and for the ethical conduct of trials.

Providing Guidance

The highly variable quality of general information available to individuals with IRDs is an important concern with the potential to impact progress in the field. Increasingly, patients rely on social media platforms for information, to connect with other families, and to learn about sponsored clinical trials. There is an urgent need for readily accessible and validated information that provides a balanced portrayal of ongoing research efforts and a realistic view of expected outcomes. In addition, many individuals with IRD would like to take advantage of readily available potential remedies but feel abandoned when it comes to the guidance needed to make safe and rational decisions, as they realize many of these may not have any real benefit. Increased efforts are needed to provide reliable information about the potentially safe, nonregulated interventions that are widely claimed to slow retinal disease, including dietary antioxidants,[132] red light,[133] light-protection,[134] electrical stimulation,[135] anti-apoptotic approaches,[40,136] as well as the mounting evidence that physical exercise may provide a benefit in IRD.[137–141] Most critically, best practices are needed for educating patients and the public on the potential dangers of direct-to-consumer treatments shown to have significant risk of harm, such as autologous nonocular tissue-derived cell therapy.[142–144]

Priorities and Recommendations for Advancing Clinical Trials

The rapidly increasing activity in clinical trials for IRDs has created a new imperative to improve the operational and ethical challenges involved in trial design, recruitment, conduct, and analysis. These challenges reflect the advanced position of IRD research in the use of gene and cell therapy, the use of highly specialized outcome measures, and the inclusion of young children in phase 1/2 trials. To identify strategies to meet these challenges and advance IRD clinical trials over the next 5 to 10 years, participants at the Monaciano-II Symposium engaged in structured discussions and multivoting to reach a consensus view of the priorities needed to accelerate progress. Each of

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the seven priorities identified, along with guidance for achieving these goals, are discussed below.

Priority 1. Using Natural History Studies to Guide Clinical Trial Design

The complexity of IRD phenotypes creates a major challenge for evaluating therapeutic efficacy using standard measures of visual performance and retinal structure. Even among individuals with the same mutation, there can be major differences in age of onset, degree of severity, and rate of progression. Without providing context relative to the natural disease course, only the most striking treatment outcomes will be demonstrably significant. In addition, there are likely to be limits on the therapeutic window of opportunity beyond which interventional efforts for a given form of therapy may have no meaningful benefit.

Natural history studies are one of the most powerful approaches for defining metrics useful for predicting disease course in a group of affected individuals. However, the difficulty in obtaining major funding, and the relatively low prevalence of IRDs, create a significant challenge, as natural history studies typically enroll relatively large numbers of patients. In addition, less than half of individuals with an IRD have a genetic diagnosis, which is a prerequisite for enrollment in most studies. Advancing this approach will involve increasing access to genetic testing, resolving variants of unknown significance, characterizing structural variants, and including standardized phenotypic data in mutation databases.

As genetically characterized IRD subpopulations are identified, broad natural history studies will be needed to identify critical time periods in disease expression and progression. A significant additional benefit is the potential identification of patient cohorts that may be included in registries and selected for future treatments. Given that such studies have taken decades in the past, achieving relevance to ongoing translational efforts will require compressing the timeline to a few years. The involvement of international consortia will be important for achieving the necessary scope and scale of patient recruitment and clinical characterization, especially for ultrarare IRDs. Strategies for improvements in the technology applied to phenotyping will also be important. These strategies may include the development and evaluation of biomarkers in patient samples, such as aqueous humor, vitreous, and blood. Long-term follow-up studies of existing trial participants will also be critical for guiding the design of future clinical studies.

Priority 2. Developing Outcome Measures Meaningful to Patients

Although the use of highly standardized clinical tests will remain a mainstay of evaluating clinical trial outcomes, metrics that evaluate whether potential treatments make a difference to the patient are critically needed. To some extent, this will require expanding beyond the use of precise clinical measurements to include the complex world of patient-reported outcomes (PROs) and performance-based tests (PBTs). The challenge will be to achieve a workable compromise between the desire for a precise measure and the need to achieve relevance to the patient experience and activities of daily living. Meeting this challenge will require defining visual activities that are meaningful to patients (e.g., reading, driving, mobility in bright or dim illumination) and that are potentially modifiable therapeutic targets. Quantifiable metrics associated with these activities, and that reflect the primary phenotype associated with the disease, can be used to assess the correlation of functional vision with clinically meaningful measures of visual function (e.g., mobility course outcomes vs. FST, pupillary light reflex, or dark-adapted perimetry). As this field develops, it will also be important to establish structure-function correlations that accurately reflect therapeutic efficacy, and to validate new outcome measures, including PROs and PBTs, using ongoing and new natural history studies of IRDs.

Priority 3. Standardizing Validated Outcome Measures

Although many outcome measures are evaluated in clinical trials for IRD, therapeutic efficacy is currently evaluated using a relatively small number of primary endpoints accepted by the FDA and/or EMA. There are no standardized guidelines that define the most useful outcome measures for evaluating various forms of treatment and IRD patient populations. In fact, some outcome measures developed by individual investigators involve unique tests and analytical methods, which have not been made available and standardized for use by others in the field. To avoid investigator bias, one important aspect of trial design is to expand testing to multiple sites. Key issues to address include identifying best strategies for developing standardized testing guidelines, defining the best surrogate outcome measures for assessing efficacy, and further establishing whether therapeutic efficacy can be generally defined or requires specific definition for each IRD, intervention, and outcome.

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Efforts to address these issues should include the input of a committee of experts working to devise guidelines for standardizing both new and existing outcome measures for individual IRDs. Possibilities include using peripheral imaging methods to provide measures of progression and the development of outcomes specific for rod function. Of particular interest is expanded use of virtual reality, artificial intelligence, and machine learning in developing new approaches to phenotyping, and for standardizing outcome measures across multiple diseases and trial sites. In addition, outcome measures and endpoints are needed that reflect the disease trajectory of individual participants rather than population-based values, as in "The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?"[145,146] It will be important to establish additional endpoints for early phase (1/2a) clinical trials that meet both regulatory requirements and correspond with disease biology and stage.

Consideration should also be given to the analysis of biomarkers, defined as "…an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[147] Although not always appropriate for use as a primary outcome measure, biomarkers of pathologic events that inform about disease status can add important disease-specific insight to the evaluation of clinical trial outcomes.

Priority 4. Reducing Inflammation Associated with IRDs and Gene Therapy for IRDs

Efforts to develop therapies for broad segments of the IRD population have focused largely on strategies that target shared pathogenetic mechanisms. The limited success so far achieved by these efforts underscores the need to better understand the mechanisms of photoreceptor cell death and survival, which differ between rod and cones, disease genes, classes of mutations, and disease stages. There is also an urgent need to prioritize the investigation of pathophysiological pathways shared among different IRDs. Among the mechanisms of interest, there is increasing awareness of the singular importance of inflammation,[141,148] which destroys tissues, compromises therapeutic outcomes, and is difficult to model, prevent, and control. Although inflammation has long been known to arise as a consequence of IRD, it has only recently been studied as a contributor to disease progression. Future needs include developing clinically relevant models of human inflammatory responses in IRD, defining the causes and mechanisms of inflammation linked to photoreceptor cell death, and evaluating the effectiveness of immunomodulation strategies relative to disease phenotype.

Immune activation and inflammation are also significant adverse events elicited by ocular administration of viral vectors and cell therapies, and thus represent serious challenges that need to be overcome to maximize efficacy while minimizing adverse events. The development of effective strategies for preventing or treating vector-induced inflammation will benefit from efforts to identify the underlying cause(s) of the inflammatory response, as well as the most effective anti-inflammatory regimens. It will also be important to define the potential impact of anti-inflammatory interventions on treatment outcomes, and to standardize their use in clinical trial protocols. Further advances will require defining which arm of the immune system is being activated, as well as the potential contributions of the viral capsid, vector DNA, and cargo protein to the inflammatory response.[149,150] Current efforts to reduce inflammation indirectly by dose sparing involve strategies to produce vector preparations with fewer empty particles, as well as directed evolution of the AAV capsid to produce vectors with increased transduction efficiency.[151]

Priority 5. Developing a Pediatric Action Plan

As children are increasingly the subjects of choice in phase 1/2 trials, it will be of paramount importance to focus on the biology and ethics of treating pediatric patients. Some therapies may only work in children, resulting in situations in which, following demonstration of safety in adults, trials may be planned for testing in children without prior evidence of efficacy in humans. A pediatric action plan for IRDs is needed that is based on collective evidence relative to disease biology and natural history, therapeutic efficacy, and safety. Elements of the plan should include development of pediatric patient registries, a network of pediatric IRD experts, and genetic counseling guidelines established with input from experts in pediatric ethics and clinical trials, which address issues discussed later.

Priority 6. Improving Advice to Patients

As clinical trials for potential therapies for IRDs are increasingly targeted to specific diseases, stages, and conditions, the vision community will need to play a central role in advising individuals about participating in these studies. Navigating this complex landscape, consisting of multiple and overlapping, gene-specific and gene-independent studies and trials, will require an understanding of the basic scientific principles being

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tested, as well as the genetic and phenotypic characteristics of the patient populations under study.

In advising individuals and families, providers should address issues relating to: privacy concerns raised by depositing patient information in shared databases; enrolling children and individuals who have relatively good visual function in treatment trials; making choices when there are multiple clinical trials or approved therapies for a given disease; the impact that participating in a clinical trial may have on the ability to participate in future trials or receive FDA- and EMA-approved treatments; and gaining access to approved therapies that may be prohibitively expensive or not covered by insurance.

To aid in decision-making, it will be important to present individuals and their families with a balanced portrayal of ongoing research efforts, realistic descriptions of the potential impact of planned interventions, assessment of the potential risks versus benefits, and that participation in early trials may be purely altruistic. This will be especially relevant when advising individuals with advanced disease, in order to convey equipoise regarding trials having uncertain safety and benefit. Transparency and informed consent will be essential for achieving beneficence in enrolling individuals who will have little to no possibility of benefiting from the treatment being tested, and who choose to participate primarily to benefit others in the future.

In the interest of improving the holistic care of individuals with IRDs, there is also an urgent need to provide up-to-date and accessible information about the safety and efficacy of dietary regimens, various forms of standard and alternative medicine, and highly experimental interventions. One such example is a cautionary statement about vitamin A supplementation in IRDs.[152] Of special concern are invasive nonregulated so called therapies, including those offered by for-profit stem-cell companies, which have only recently fallen under regulatory jurisdiction by the FDA, and have no proven benefit.[153] In almost all cases, these approaches raise issues beyond the expertise of community physicians and health care providers, and should be addressed by IRD specialists.

Priority 7. Promoting Transparency, Accountability, and Accessibility

IRD clinical trials are currently being conducted, in large part, in North America and the European Union, with recent expansion of some studies more globally. This reflects the small number of IRD specialists having the background, experience, and staff needed to design and conduct trials, the availability of suitably characterized IRD subjects, and the difficulty in obtaining major funding. As a result, the conduct of multiple trials currently relies on a core group of individuals, some of whom may have a conflict of interest. Individuals in academics publicly declare their conflicts of interest, which are managed by their universities using a robust system of checks and balances. Nevertheless, there is significant corporate involvement in multiple aspects of trial design, data management, and analysis, which can foster a culture of nontransparency that works against timely and full disclosure of outcomes.

Although sponsors are mandated by law to inform regulatory bodies of safety issues and serious adverse events, and orphan drug designation requires public data sharing, other clinically relevant findings may not be revealed, or their significance obscured when combined with other data. Improvements to the accountability framework are needed that foster transparency between clinical trial investigators and sponsors. This should include mechanisms for reporting clinical trials information that is not limited by sponsor interests (e.g., potentially involving negative results or safety issues), and for releasing the results of clinical trials regardless of the therapeutic potential. Useful components of such mechanisms include data masking and information aggregation, potentially facilitated by academic and industry consortia.

A major factor currently limiting the capacity of ongoing trials, and the ability to initiate new ones, is the small number of IRD centers that have the required expertise and infrastructure. Additional challenges include poor reimbursement for visual function tests, the time needed for patients to decide to participate, limited financial compensation for patients who do participate, and managing unduly optimistic patient expectations. Increasing clinical trials, particularly in underserved countries, will require increasing support for developing centers of excellence, and for training additional IRD and clinical trials experts. Such efforts are currently hampered by lack of the structure and funding needed to support fellowship training and training grants, and for the development of culture- and language-specific tools and resources for the identification and enrollment of patients. A critical benefit likely to result from improving patient access to well-regulated and monitored clinical trials is the potential for reducing patient experimentation with potentially unsafe interventions.

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Conclusions and Future Prospects

IRDs have long been viewed as a group of disorders for which there are no treatments or cures. This maxim is now being overturned by the extraordinary efforts of vision scientists and clinicians, resulting in an exciting cohort of clinical trials based on sound preclinical data. Although these efforts are still evolving, the possibilities for making a significant impact on the lives of individuals with IRDs has never been greater. Advances in DNA and RNA therapies, cell transplantation, and combinatorial therapeutics are expected to be major drivers moving forward. Improved understanding of disease etiology and the potential for targeting shared pathology are poised to transition the focus from gene-specific therapies to genetically informed therapies with broader reach. Opportunities for clinical efforts to synergize with technological advances are rapidly emerging from the use of big data analytics that improve the predictive value of genetic diagnostics, the use of machine learning and artificial intelligence to improve imaging analysis and individualized outcomes, and the use of virtual reality to develop new approaches to phenotyping and standardizing outcome measures.

The expanding reach of IRD clinical trials, including access to unique patient populations, is creating exciting new opportunities for research and treatment, while also highlighting the need to train increased numbers of international IRD experts. Access to trusted information, including a balanced portrayal of ongoing research efforts and expectations for clinical trials, is strengthening the environment in which clinicians and individuals are making critical health care decisions. Above all, this progress is changing attitudes about the possibility of developing effective therapies for blinding diseases, while serving as a constant reminder of the importance of remaining focused on the ethical concerns, quality of life, and human stories of individuals with IRDs.

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