Title

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Journal

RETINA: The Journal of Retinal and Vitreous Diseases, 45(2)

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Publication Date

2025-02-01

DOI

10.1097/IAE.0000000000004296

Peer reviewed

OPEN

THE FIGHT INHERITED RETINAL BLINDNESS! PROJECT

A New Treatment Outcome and Natural History Registry for Inherited Retinal Disease

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Purpose: To design and build a new disease registry to track the natural history and outcomes of approved gene therapy in patients with inherited retinal diseases.

Methods: A core committee of six members was convened to oversee the construction of the Fight Inherited Retinal Blindness! module. A further 11 experts formed a steering committee, which discussed disease classification and variables to form minimum datasets using a consensus approach.

Results: The web-based Fight Inherited Retinal Blindness! registry records baseline demographic, clinical, and genetic data together with follow-up data. The Human Phenotype Ontology and Monarch Disease Ontology nomenclature were incorporated within the Fight Inherited Retinal Blindness! architecture to standardize nomenclature. The registry software assigns individual diagnoses to one of seven broad phenotypic groups, with minimum datasets dependent on the broad phenotypic group. In addition, minimum datasets were agreed on for patients undergoing approved gene therapy with voretigene neparvovec (Luxturna). New patient entries can be completed in 5 minutes, and follow-up data can be entered in 2 minutes.

Conclusion: Fight Inherited Retinal Blindness! is an organized, web-based system that uses observational study methods to collect uniform data from patients with inherited retinal disease to track natural history and (uniquely) treatment outcomes. It is free to users who have control over their data.

RETINA 45:286–295, 2025

The past three decades have seen unprecedented advances in our knowledge of the genetic causes, pathways to blindness, and potential treatments for inherited retinal diseases (IRDs).[1–3] The prospect of new and emerging therapies for IRDs has also necessitated a reexamination of the natural history of IRDs in prospective cohort studies. This has been driven by the need to identify appropriate biomarkers for disease progression, which might serve as appropriate outcome measures in trials of emerging treatments[4] Advances in molecular biology, vector construct technology, and surgical delivery have led to the successful development of the first effective gene replacement therapy for an IRD. Voretigene neparvovec (Luxturna) gene replacement for patients with autosomal recessive *RPE65*-associated IRD, demonstrated efficacy in its pivotal/Phase III clinical trial and subsequently gained Food and Drug Administration approval in 2017.[5,6] Furthermore, it is likely that other effective therapies will reach the clinic in the next few years,

highlighting the need to develop standardized methods of assessment and recording real-world data.

Prospective cohort studies and clinical trials enroll participants who fulfil specific entry requirements but who may not be truly representative of the spectrum of individuals with a particular disease. Therefore, as new treatments become available—such as voretigene neparvovec *RPE65* gene replacement therapy for LCA2/*RPE65*-associated IRD—there is a need for postmarketing surveillance or so-called Phase IV clinical trials to demonstrate "real-life" safety and efficacy,[5–8] especially given recent reports of chorioretinal atrophy after treatment.[9–11] Evidence gleaned from Phase IV studies has previously led to the withdrawal of medications demonstrating promise in Phase III studies[12] and have highlighted adverse events not identified in individual randomized controlled trials.[13]

The phenotypic heterogeneity and the >300 genes associated with IRDs poses a tremendous challenge for developing treatments.[14] Thus, different aspects of visual function may better characterize patients with different IRD phenotypes. Furthermore, tests of vision may need to be adapted to severity of vision impairment over time with disease progression. For example, tests of vision at—or close to—fixation may only detect changes in the later stages of IRDs, which commence in the retinal periphery. Notably, large natural history studies could conceivably identify critical periods of specific IRDs in which certain aspects of visual function are compromised. This in turn may identify target populations for enrolment in future clinical trials of emerging therapies.[15]

Here, we outline the creation of the Fight Inherited Retinal Blindness! (FIRB!) Registry module, an efficient web-based means of collecting and tracking clinical data and treatment outcomes in patients with IRDs. The registry builds on previous modules housed with the Save Sight Registries, which were initially designed and conceived to monitor outcomes in patients receiving anti–vascular endothelial growth factor agents for managing neovascular age-related macular degeneration.[12] The FIRB! module aims to efficiently capture pertinent data that can characterize and track structural and functional measures and quality of life in patients with IRDs. In addition, the registry will track natural history and monitor treatment outcomes with approved therapies as they become available (currently limited to voretigene neparvovec).[6]

Methods

Project Structure

The FIRB! consists of a core supervising committee and a steering committee. The core supervising committee comprises six members with an interest in IRDs and/or disease registries (M.P.S., A.T.M., J.G., P.S., D.B., and M.C.G.). This committee was responsible for the inception and implementation of the FIRB! registry. The broader steering committee comprises 11 members, all of whom have a clinical and/or research interest in IRDs. "Users" are defined as clinicians or groups using the registry to enter patient data, and "participants" are individual patients whose data are tracked.

Initially, two core committee meetings outlined the remit of the module. As a first aim, the need to track real-world outcomes for patients undergoing approved gene therapy was identified. Second, the committee recognized the benefits of tracking the natural history of IRDs to help improve our understanding of disease course and to identify critical time points for potential interventions. A further three core committee meetings were held after the steering committee meeting discussed below.

A first meeting of the steering committee was convened to discuss the classification of IRDs within the module and the possible variables to be considered for inclusion as minimum datasets. After this initial meeting, questionnaires were then sent to steering committee members for their opinion on whether individual variables should—or should not—be

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Part of the development of this module was funded by a Grant provided to the University of Sydney by Novartis.

None of the authors has any financial/conflicting interests to disclose.

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included as part of a minimum dataset. In line with other Save Sight Registries, a consensus approach was used, whereby variables were only deemed to form part of minimum datasets if 100% concordance was achieved.

The results of steering committee meetings informed the construction of the FIRB! module, a web-based registry (https://savesightregistries.org). The module uses similar software and programming approaches to those previously described.[12] After the build of the initial module, feedback was sought from a subset of steering committee members before formal launch.

Results

Nomenclature & Disease Classification

The initial core committee meeting addressed critical issues for efficiently capturing pertinent data in patients with IRD. Because of phenotypic heterogeneity and varied nomenclature, discussion centered around a standardized taxonomy and minimum datasets. To standardize terminology, Human Phenotype Ontology[16] and the Monarch Disease Ontology (MONDO) nomenclature were adopted.[17] Broad phenotypic classifications were also agreed on to permit efficient and appropriate data capture (Table 1). A subsequent steering committee meeting to shortlist the appropriate data fields and to consider minimum datasets for the relevant clinical entities was held (see below).

Agreed Data Fields

Baseline data include demographic data, smoking status, mode of inheritance, causative gene(s); if known, zygosity, other gene abnormalities, mutation type(s), and family history (Figure 1) are entered to create a unique entry for an individual patient. Other pertinent patient information are recorded at the visit level, including working diagnosis, systemic history/features (including systemic modifiers as part of a syndromic IRD), previous IRD treatments, previous ophthalmic procedures (including cataract surgery), and other ophthalmic conditions (including refractive error; Figure 2).

The steering committee-agreed parameters for tracking structure and function in the FIRB! module are as follows: visual acuity, visual field, color vision, optical coherence tomography, fundus autofluorescence imaging, and electrodiagnostic parameters.

Data for visual acuity can be entered in the preferred format (e.g., Snellen fraction, log minimum angle of resolution (logMAR)) and for the preferred chart of the user. For example, data for visual acuities of counting fingers or hand motions are converted by the software (Table 2) to the equivalent in letters (i.e., for a Bailey–Lovie style letter chart) and can be presented graphically in the preferred format of the user (Figure 3).

Visual field data are problematic insofar that sensitivity estimates from different instruments may not be comparable because of differences in stimulus and background parameters. Furthermore, instruments differ in their algorithms for determining stimulus thresholds. In recognition of this—and broadly in keeping with the Save Sight Glaucoma Registry[18]—only key indices are recorded, and a variety of testing strategies are permitted: the 30-2 testing approach (mean deviation and pattern SD recorded), the 10-2 microperimetric approach (mean sensitivity), and kinetic perimetry (IIIe and Ve stimuli total area in deg2). In addition, full-field sensitivity testing (FST)[19–21] results may be captured by the module including the device used and test target (white, blue, red) in selected participants (see below).

Structural measures can be recorded using optical coherence tomography and fundus autofluorescence imaging. Optical coherence tomography parameters recordable include central foveal thickness (μm), macular volume (μm^3), ellipsoid zone width (mm), and presence/absence of cystoid macular edema. The fundus autofluorescence parameters captured are the width of the autofluorescent ring (where present) and absence or low levels of fundus autofluorescence signal (which may indicate visual cycle defects). At present, images themselves cannot be uploaded, although it is envisaged that in the future, image analysis may be incorporated into the registry in a legislation-compliant fashion.

Dyschromatopsia is a key feature of IRDs affecting the cone photoreceptors, and performance at clinical color vision tests can be recorded with the FIRB! module. Users have the option of including a variety of tests that are capable of characterizing both red/green and tritan color discrimination. These include the Farnsworth–Munsell tests and their derivatives, including the (FM) D15, enlarged D15, the FM 100Hue and the Roth 28 Hue. In addition, users may record results at the Hardy–Rand–Rittler plates.

Electrodiagnostic testing is important in diagnosing and monitoring many IRDs and is included in the functional measures in the FIRB! registry. Data include the instrument used for performing tests and photopic and scotopic a- and b-wave amplitudes (% of mean normal for the device used). In addition, users can input whether any pathognomonic changes are evident (e.g., supranormal scotopic b-wave in *KCNV2*-related retinopathy).

Table 1. Broad Classification of Phenotypes Within the FIRB! Architecture

Category/Subcategory	HPO	Display Name	Tooltip
Rod–cone dystrophy	HP:0000510	Rod–cone dystrophy	Syn. retinitis pigmentosa, including HPO generalized, sectoral and pericentral
Rod–cone dystrophy—enhanced S-cone syndrome	HP:0000510—MONDO:0100288	Enhanced S-cone syndrome	
Congenital stationary night blindness (CSNB)	HP:0007642	CSNB	
Congenital stationary night blindness—Oguchi disease	HP:0030639 – MONDO:0019152	Oguchi disease	
Congenital stationary night blindness—fundus albipunctatus	HP:0030642	Fundus albipunctatus	
Cone/cone–rod dystrophy	HP:0000548	Cone/cone–rod dystrophy	
Congenital cone dysfunction disorder—achromatopsia	HP:0011516	Achromatopsia	syn. rod monochromacy
Congenital cone dysfunction disorder—blue cone monochromacy	HP:0007939	Blue cone monochromacy	syn. S-cone monochromacy, X-linked incomplete achromatopsia
Congenital cone dysfunction disorder	HP:0030637	Congenital cone dysfunction disorder (unspecified)	
Retinal dystrophy—Stargardt disease	HP:0000556—ONDO:0019353	Likely/confirmed *ABCA4*-related retinopathy	Including Stargardt disease and Stargardt-like phenotypes
Retinal dystrophy—pattern dystrophy of the retina	HP:0007963	Pattern dystrophy	
Retinal dystrophy—retinal/macular dystrophy with vitelliform-like retinal lesions	HP:0000556 and HP:0030643	Bestrophinopathy	Including best disease and autosomal recessive bestrophinopathy (ARB)
Retinal dystrophy—Doyne honeycomb retinal dystrophy	HP:0000556—MONDO:0007471	Familial dominant drusen	Syn. Doyne honeycomb retinal dystrophy and malattia leventinese
Macular dystrophy—North Carolina macular dystrophy	HP:0007754—MONDO:0007630	North Carolina macular dystrophy	
Macular dystrophy	HP:0007754	Macular dystrophy (unspecified)	
Chorioretinal dystrophy—choroideremia	HP:0001139	Choroideremia	
Chorioretinal dystrophy—gyrate atrophy	HP:0001135—MONDO:0009796	Gyrate atrophy	
Chorioretinal dystrophy—Bietti crystalline dystrophy	HP:0001135—MONDO:0008865	Bietti crystalline dystrophy	
Chorioretinal dystrophy	HP:0001135	Chorioretinal dystrophy (unspecified)	
Vitreoretinopathy (hereditary)—exudative	HP:0030490	FEVR	Including familial exudative vitreoretinopathy, Norrie disease
Vitreoretinopathy (hereditary)—degenerative	HP:0007964	Degenerative vitreoretinopathy	Including Stickler, Wagner, Marshall
Retinal dystrophy—retinoschisis	HP:0030502	Retinoschisis	
Retinal dystrophy—Leber congenital amaurosis	HP:0000556—MONDO:0018998	Leber congenital amaurosis	
Retinal dystrophy—Sorsby fundus dystrophy	HP:0000556—MONDO:0007640	Sorsby fundus dystrophy	
Retinal dystrophy—LORD	HP:0000556—MONDO:0011579	Late-onset retinal degeneration	
Retinal dystrophy	HP:0000556—	Retinal dystrophy (unspecified) *triggers free text*	

Users can select a diagnosis based on human phenotype ontology nomenclature. Each selectable diagnosis is ascribed to a broad phenotypic group by the FIRB! software, which in turn determines the minimum dataset (see text for details).

HPO, human phenotype ontology; MONDO, monarch disease ontology.

Minimum Datasets

Members of the steering committee were contacted independently for feedback on the minimum dataset for each broad phenotypic category (responses summarized in Table 3). Because the FIRB! software will only "count" fully completed data entries, any given data field was only considered part of the minimum dataset when there was 100% concordance among the steering committee. Other variables can be included by users (should they wish), but these do not form part of the minimum dataset.

Treatment Outcomes—Voretigene Neparvovec Gene Therapy

Voretigene neparvovec subretinal gene therapy has been approved in multiple jurisdictions for the treatment of IRD caused by biallelic mutations to the *RPE65* gene. The pivotal trials of this treatment suggest that it confers profound improvements in retinal sensitivity—on average 2.1 log units on FST.[6] This translates to meaningful improvements in tasks simulating activities of daily living—in particular, similar improvements were seen in the minimum illuminance required to navigate a specially designed obstacle course (the multiple luminance mobility test).[22] However—for reasons outlined above—there is a need to track real-world outcomes and possible unforeseen side effects after subretinal voretigene neparvovec *RPE65* gene replacement therapy in patients with biallelic pathogenic mutations to the *RPE65* gene. Evidence garnered from real-world studies has previously led to the withdrawal of medications demonstrating promise in Phase III studies[12] and has highlighted rare but important complications.[13] In the context of Luxturna gene therapy, postregulatory reports have highlighted a hitherto unrecognized complication of treatment: chorioretinal atrophy.[9–11] This complication may occur in up to 50% of eyes undergoing Luxturna gene therapy[9] and is reported to be preceded by alterations on short-wavelength fundus autofluorescence imaging.[11] The FIRB! registry provides an easy, convenient and rapid means of tracking treatment outcomes, in addition to facilitating the monitoring of such treatment complications, on an international scale.

Quality of Life

The FIRB! includes validated patient-reported outcomes in the form of the Impact of Vision Impairment questionnaire as part of the module, in line with the other Save Sight Registry Modules.

Patient and Public Involvement

Patients and the public were not engaged in selecting the recorded variables of the module per se. However, patients were involved in developing the quality of life metrics instituted in the FIRB! registry. Furthermore, the local research ethics committee (South Eastern Sydney Local Health District) has patient representatives on its review panel.

Data Anonymity and Security

In line with all other Save Sight Registry Modules (see https://savesightregistries.org), data anonymity and security are maximized by generating a unique string of identifiers (letters and numbers) for each

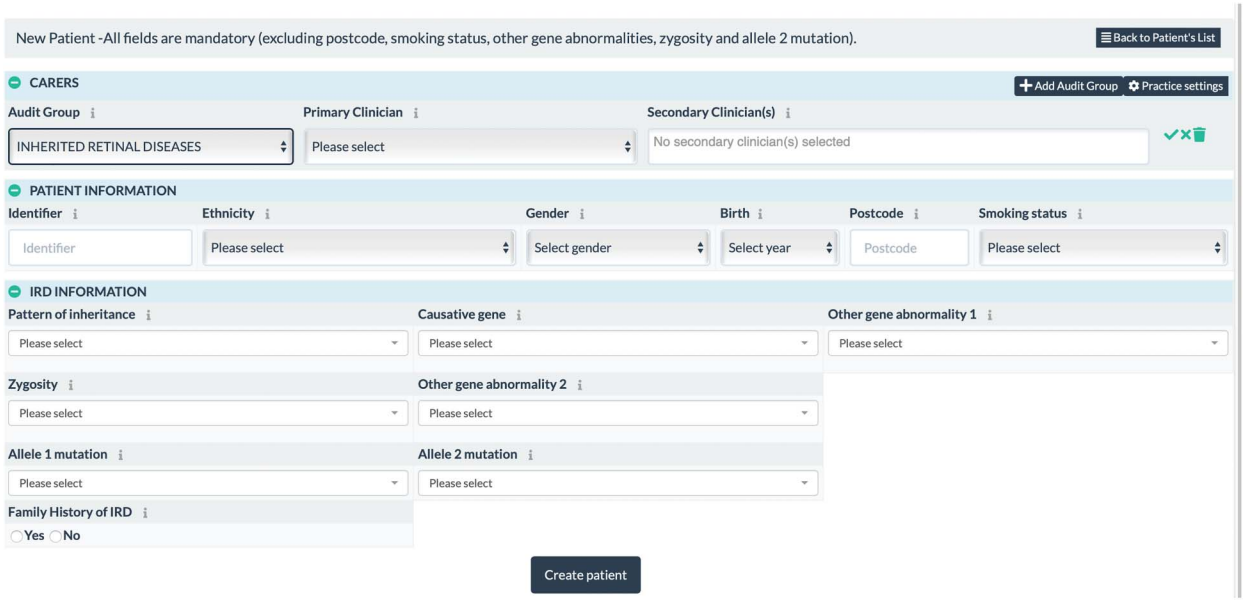

Fig. 1. Screen grab of the patient detail entry page from the Fight Inherited Retinal Blindness! registry.

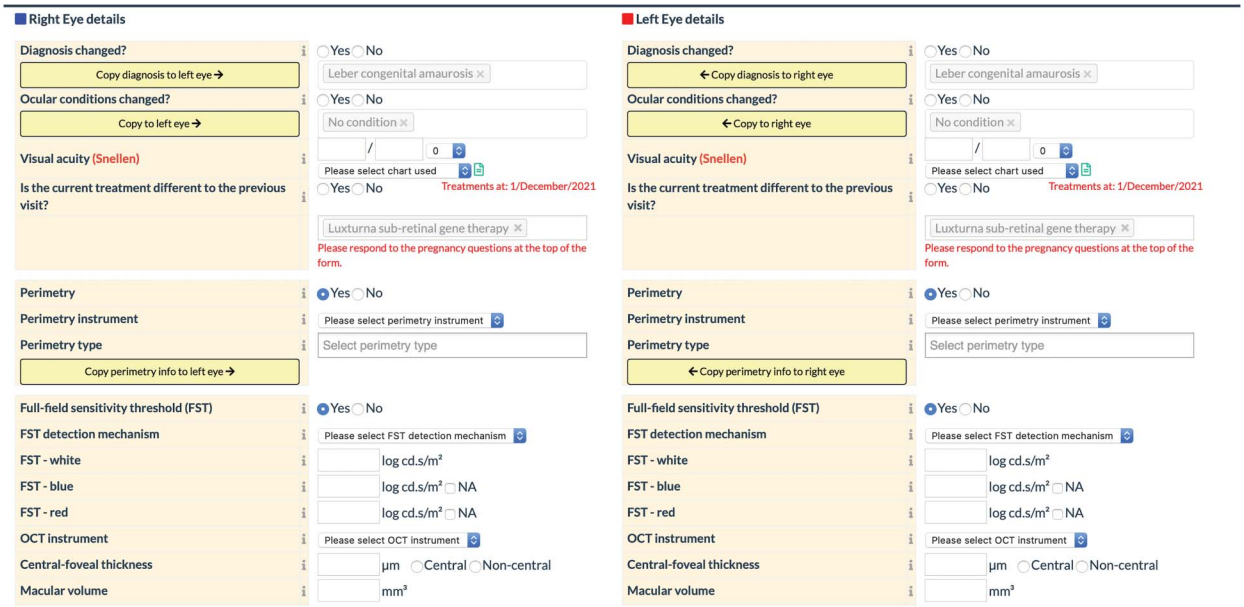

Fig. 2. Screengrab of a visit entry page for a patient in the FIRB!.

participant. Although this string is not directly visible to users, it is linked to their practice identifiers. When entering patient follow-up data, the user's practice identifier may be selected to create a follow-up visit. To ensure that the correct data are entered for individual patients, their initials and date of birth are displayed clearly. Demographic data are also stored within the system for each participant, including gender, date of birth, initials, and ethnicity. Data transmission is protected through 128-bit encryption (Secure Sockets Layer), and all data are stored and backed up on the University of Sydney's Information and Communication Technology Department's secure servers.

The identity of users is also protected; however, users may view their own data together with summary data for their own country to permit comparison. The Registry is designed so that individual users have full access and control—or "ownership"—of their data, which they can analyze as they prefer and/or combine with other users' data for analysis and publication. Furthermore, users may withdraw their data at any juncture without providing a reason for doing so.

Ethics

Clinical registries fall under the umbrella of quality assurance activities, which are considered an integral part of healthcare. As a research activity, the FIRB! module adheres to the tenets of the Declaration of Helsinki and has been approved by the Local Health Research Ethics Committee (HREC ETH00956). Similarly, overarching ethics approval has been gained from the Royal Australian and New Zealand College of Ophthalmologists' Research Ethics Committee, which provides coverage for practices within Australia and New Zealand (ethics approval Ethics 16.09). Despite this, the data captured by the module are those that clinicians will usually capture during routine clinical care. This, combined with the fact that the registry represents a quality assurance activity, means that individual ethical approval may not strictly be required, provided that patients within a practice have consented to the use of anonymized data to be used for clinical audit and research purposes. Although the detail with which genetic information is recorded does not make patients identifiable, the steering committee's view is that mutations to specific genes are infrequent enough to demand that a patient's consent is required as part of the FIRB! module.

Data Representation and Export

Users may view timeline plots of individual variables for participants (e.g., best-corrected visual acuity vs. date or vs. age). In addition, each user may download datasets in comma-separated variable (csv) format. Again, csv files will include means of combining and comparing data entries by standardizing outputs (e.g., using participant age instead of the date of entry alone). Users can scrutinize and analyze such data in whichever way they see fit.

The steering committee agreed by consensus for HPO- and MONDO-based nomenclature to underlie

Table 2. Visual Acuity Conversions Within the FIRB! Software

Snellen	ETDRS	LogMAR	Snellen	ETDRS	LogMAR
NPL	0	2.9	**6/36**	46	0.78
PL	0	2.6		47	0.76
HM	0	2.3		48	0.74
CF	0	2.0		49	0.72
6/379	0	1.80	**6/30**	50	0.70
6/360	0	1.78		51	0.68
	0	1.76		52	0.66
	0	1.74		53	0.64
	0	1.72		54	0.62
6/300	0	1.7	**6/24**	55	0.60
	1	1.68		56	0.58
	2	1.66		57	0.56
	3	1.64		58	0.54
	4	1.62		59	0.52
6/240	5	1.60	**6/19**	60	0.50
	6	1.58	**6/18**	61	0.48
	7	1.56		62	0.46
	8	1.54		63	0.44
	9	1.52		64	0.42
6/190	10	1.50	**6/15**	65	0.40
6/180	11	1.48		66	0.38
	12	1.46		67	0.36
	13	1.44		68	0.34
	14	1.42		69	0.32
6/150	15	1.40	**6/12**	70	0.3
	16	1.38		71	0.28
	17	1.36		72	0.26
	18	1.34		73	0.24
	19	1.32		74	0.22
6/120	20	1.30	**6/9.5**	75	0.20
	21	1.28	**6/9**	76	0.18
	22	1.26		77	0.16
	23	1.24		78	0.14
	24	1.22		79	0.12
6/95	25	1.2	**6/7.6**	80	0.1
6/90	26	1.18		81	0.08
	27	1.16		82	0.06
	28	1.14		83	0.04
	29	1.12		84	0.02
6/76	30	1.1	**6/6**	85	0
5/60	31	1.08	**6/5**	86	−0.02
	32	1.06		87	−0.04
	33	1.04		88	−0.06
	34	1.02		89	−0.08
6/60	35	1.0	**6/4.8**	90	−0.10
	36	0.98		91	−0.12
	37	0.96		92	−0.14
	38	0.94		93	−0.16
	39	0.92		94	−0.18
6/48	40	0.9	**6/3.8**	95	−0.20
	41	0.88		96	−0.22
	42	0.86		97	−0.24
	43	0.84		98	−0.26
	44	0.82		99	−0.28
6/38	45	0.80	**6/3**	100	−0.30

The bold values are Snellen fractions.

Snellen, Snellen fraction; ETDRS, standardized letter score on the "Early Treatment of Diabetic Retinopathy Study" (ETDRS) Bailey–Lovie style letter chart; logMAR, base 10 logarithm of the minimum angle of resolution.

Fig. 3. Screengrab of a data entry/presentation page for a patient with IRD secondary to biallelic *RPE65* mutations after retinal gene therapy with voretigene neparvovec. Pertinent clinical data (e.g., best-corrected visual acuity, FST results) can be plotted against time as a means of easily tracking disease progression and treatment effects.

the user interface; a broad phenotypic classification and relevant minimum datasets were also agreed as outlined above (Table 3).

An important function of the FIRB! module is to monitor real-world outcomes of gene and other emerging therapies as they become available. At present, one retinal gene therapy has received regulatory approval in multiple jurisdictions: voretigene neparvovec. The steering committee determined that the minimum dataset for patients undergoing this treatment should include the outcome measures of best-corrected visual acuity, visual field (using the preferred method at the practice site), FST, and optical coherence tomography. In addition, it was deemed essential that the FIRB! records all adverse events and serious adverse events after treatment, and pregnancy outcomes, where relevant.

Initial patient data entry screen is seen in Figure 1 and consists of baseline medical and ophthalmic data.

Table 3. Minimum Datasets for Each Broad Phenotypic Group

Phenotype/Data	VA	Perimetry	Color vision	OCT	FAF	EDT
Macular dystrophy	**100** (12–18 months)	45	91	**100** (12–18 months)	**100** (12–18 months)	**100** (baseline)
Cone dysfunction syndrome	**100** (12–18 months)	55	**100** (12–18 months)	**100** (12–18 months)	**100** (12–18 months)	**100** (baseline/5 years)
Cone & cone–rod dystrophy	**100** (12–18 months)	64	**100** (BL/3 years)	**100** (12–18 months)	**100** (12–18 months)	**100** (baseline)
Rod–cone dystrophy	**100** (12–18 months)	91	55	**100** (12–18 months)	**100** (12–18 months)	**100** (baseline)
Rod system dysfunction syndrome/congenital stationary night blindness	**100** (12–18 months)	64	64	**100** (12–18 months)	**100** (12–18 months)	**100** (baseline)
Chorioretinal dystrophy	**100** (12–18 months)	82	64	**100** (12–18 months)	**100** (12–18 months)	91
Hereditary vitreoretinopathy	**100** (12–18 months)	36	36	**100** (12–18 months)	**100** (12–18 months)	55

Percentages of responses supporting inclusion of each variable as part of a minimum dataset are given, along with the recommended frequency of repeat assessment. Where 100% agreement is reached, the variable was included in the registry as part of the minimum dataset.

EDT, electrodiagnostic testing; FAF, fundus autofluorescence.

The follow-up visit data entry screen in Figure 2; it seeks to capture changes over time in minimum datasets and to record any new ophthalmic or treatment interventions as they occur. In addition to tracking visual acuity over time (Figure 3), the graphical display feature of the module permits the tracking of other outcome measures over time, such as FST, visual field data, etc. When entered by an experienced allied health professional, initial visit data can be input in less than 5 minutes and follow-up visits can be completed within 2 minutes.

This module is free for users and access can be obtained by following the instructions at the Save Sight Registries Web site: https://savesightregistries.org/fight-inherited-retinal-blindness/.

Free training in the use of the module is provided.

Discussion

The Fight Inherited Retinal Blindness Registry! was conceived for two purposes: first, to track the natural history of IRDs, and second, to monitor real-world outcomes in patients receiving emerging treatments, such as gene therapy. It will be noted that there are several antecedent IRD international registries that are aimed primarily at tracking the natural history of IRD, including the Foundation Fight Blindness' "My Retinal Tracker."[23] To deal with the phenotypic diversity of IRDs,[2] the registry uses standardized nomenclature, based on the Human Phenotype Ontology project,[16] for categorization, which in turn will facilitate comparison, or data combination, with other registries internationally (e.g., the Foundation Fighting Blindness' "My Retina Tracker").

The FIRB! registry assigns each unique diagnosis into a phenotypic category, which in turn determines the minimum dataset required to be input by users. A consensus agreement among steering committee members determined the datasets. The required fields were set as the minimum amount of data deemed necessary, although additional data fields are available for users who wish to collect such data on their own patients. It is anticipated that this strategy will maximize the utility of the registry by minimizing missing data/nonincluded data while facilitating the uptake of the registry by offering additional fields to users who wish to track these data in their own patients. The minimum dataset for patients undergoing voretigene neparvovec gene therapy is driven by the requirements of regulatory bodies to track real-life outcomes in patients with IRD caused by biallelic *RPE65* mutations. In general, patient encounters for patients with IRD are longer than for patients with other forms of retinal disease, with a greater burden on patients and clinicians regarding consultation times and ancillary testing. Nevertheless, the input of data fields in the FIRB! registry is not overly lengthy: initial visit data can be entered in less than 5 minutes and follow-up visits can be completed within 2 minutes, provided the data are to hand.

Tracking the natural history of large groups of patients with IRD may highlight critical periods in which certain aspects of vision deteriorate over short periods. In turn, this may inform researchers as to optimum periods for intervening with emerging treatments as they become available. Indeed, given the recent failure of highly promising therapies to meet their primary endpoints in clinical trials,[24] the identification of such periods may be crucial in proving the efficacy of such interventions.

This FIRB! registry provides a rapid means of recording outcomes after Luxturna gene therapy. These outcome measures are those recommended by both regulatory authorities[25] and professional bodies internationally,[26] making the registry a convenient and rapid means of recording outcomes to assess real-world outcomes and for drug monitoring by national authorities. Furthermore, FIRB! provides a means of tracking adverse or unanticipated events—such as the development of chorioretinal atrophy—which has only been reported post regulatory approval in a significant minority of patients undergoing voretigene neparvovec gene therapy.

Key words: inherited retinal disease, gene therapy, retinitis pigmentosa, voretigene neparvovec, registries, real-world outcomes.

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