Foundation Fighting Blindness (FFB) Consortium

Universal Rare Gene Study: A Registry and Natural History Study of Retinal Dystrophies Associated with Rare Disease-Causing Genetic Variants

Protocol Identifying Number: Uni-Rare

Funded by: Foundation Fighting Blindness

Version Number: 1.2

12DEC2022

Key Roles and Signature Page
Universal Rare Gene Study

Protocol Identifying Number: Uni-Rare

Version Number: v1.2

12DEC2022

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADRP	Autosomal Dominant Retinitis Pigmentosa
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BRVT	Berkeley Rudimentary Vision Test
CC	Coordinating Center
CFR	Code of Federal Regulations
CGA	Central Genetics Auditor
CI	Confidence Interval
CME	Cystoid Macular Edema
CRF	Case Report Form
DHA	Docosahexaenoic Acid
EC	Ethics Committee
eCRF	Electronic Case Report Form
ERG	Electroretinogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
EVA	Electronic Visual Acuity
EZ	Ellipsoid Zone
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FFB	Foundation Fighting Blindness
ffERG	Full-field Electroretinogram
FST	Full-field Stimulus Threshold
GC	Genetics Committee
GCP	Good Clinical Practice
HOV	Hill of Vision
HRPP	Human Research Protection Program
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRD	Inherited Retinal Degeneration
KP	Kinetic Perimetry
LAR	Legally Authorized Representative
LLVA	Low Luminance Visual Acuity
LVP-FVQ II	L.V. Prasad-Functional Vision Questionnaire

ABBREVIATION	DEFINITION
MedDRA	Medical Dictionary for Regulatory Activities
MP	Microperimetry
MRDQ	Michigan Retinal Degeneration Questionnaire
N	Number or Sample Size
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
OU	Both Eyes
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcome
PROMIS®-29	Patient-Reported Outcomes Measurement Information System
QA	Quality Assurance
QC	Quality Control
r	Pearson Correlation Coefficient
RC	Reading Center
RD	Retinal Dystrophy
RBM	Risk-Based Monitoring
RP	Retinitis Pigmentosa
RUSH2A	Rate of Progression in USH2A Related Retinal Degeneration Study
SAE	Serious Adverse Event
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SP	Static Perimetry
ULV-VFQ-50	Ultra Low Vision-Visual Functioning Questionnaire
VA	Visual Acuity
VF	Visual Field
ViSIO-PRO	Visual Symptom and Impact Outcomes-Patient Reported Outcome
ViSIO-ObsRO	Visual Symptom and Impact Outcomes-Observer Reported Outcome
V_{tot}	Total Volume
VUS	Variant(s) of Unknown Significance
YAC	Younger Age Cohort
α	Type I Error

PROTOCOL OUTLINE

CATEGORY	DESCRIPTION
Title	**Universal Rare Gene Study**: A Registry and Natural History Study of Retinal Dystrophies Associated with Rare Disease-Causing Genetic Variants
Abbreviated Name	Uni-Rare
Number of Sites	Approximately 40
Study Design	There are two components of this international, multicenter study: **Registry** • A standardized genetic screening and a prospective, standardized, cross-sectional clinical data collection • Enrollment is open to all genes on the **RD Rare Gene List** **Natural History Study** • A prospective, standardized, longitudinal Natural History Study • Enrollment opens gene-by-gene, based on funding and within-gene Registry enrollment
Objectives	The study objectives are as follows. See section 1.3 for details. **Registry Objectives** 1. Genotype Characterization 2. Cross-Sectional Phenotype Characterization (within gene) 3. Establish a Link to My Retina Tracker Registry (MRTR) 4. Ancillary Exploratory Studies – Pooling of Genes **Natural History Study Objectives** 1. Natural History (within gene) 2. Structure-Function Relationship (within gene) 3. Risk Factors for Progression (within gene) 4. Ancillary Exploratory Studies – Pooling of Genes
Précis	The **Registry** will establish genetically and clinically well-characterized cohorts of patients across hundreds of genetic variants associated with retinal dystrophy (RD). Characterization of these patients will accelerate eligibility screening for the Natural History Study, provide cross-sectional data on phenotype-genotype associations, and contribute to our knowledge of pathogenicity of these rare disease-causing variants. The **Natural History Study** will accelerate the identification and development of sensitive, reliable outcome measures for clinical trials, which will facilitate development of treatments for retinal dystrophies due to disease-causing genetic variants. The expected impact of the Natural History Study is as follows: 1. Describe the natural history of retinal degeneration in patients with rare disease-causing genetic variants 2. Identify sensitive structural and functional outcome measures to use for future multicenter clinical trials of rare inherited retinal degeneration

<table>
<tr><th>CATEGORY</th><th>DESCRIPTION</th></tr>
<tr><td></td><td>3. Identify well-defined subpopulations for future clinical trials of investigative treatments for rare inherited retinal degeneration</td></tr>
<tr><td>Participant Duration</td><td><u>Registry</u>
Registry/Screening Visit: Approximately 1-90 days
Genetic screening: Approximately 30 days
Annual phone calls: Up to approximately 48 months (<u>or</u> until gene is moved to the Natural History Study)
<u>Natural History Study</u>
Baseline Visit to 48-Month Follow-up Visit: Approximately 48 Months</td></tr>
<tr><td>Younger Age Cohort</td><td>Participants ages ≥ 4 years and < 8 years old will be designated as the Younger Age Cohort.
Participants in this cohort will not be assigned a Vision Cohort.
Registry/Screening Visit and Natural History Study Visits will have an abbreviated testing schedule, detailed in the Schedule of Study Visits and Procedures table.</td></tr>
<tr><td>Vision Cohorts</td><td>Participants who are aged ≥ 8 years old will be designated into one of the following Vision Cohorts based on data in the better eye, at the Registry/Screening Visit. See section 2.2 for the detailed definitions.<table><tr><th></th><th>VF diameter ≥10° in every meridian</th><th>VF diameter <10° in any meridian</th></tr><tr><td>20/80 or better</td><td>Vision Cohort 1</td><td>Vision Cohort 2</td></tr><tr><td>20/100-20/400</td><td>Vision Cohort 2</td><td>Vision Cohort 2</td></tr><tr><td>20/500 or worse</td><td>Vision Cohort 3</td><td>Vision Cohort 3</td></tr></table></td></tr>
<tr><td>Protocol Overview</td><td>The protocol overview is as follows. Also see flow charts in next section.
<u>Screening Phase</u>
Review patient’s current genetic report* as having at least one gene on the RD Rare Gene List meeting one of the eligible Genetic Screening Criteria and review other eligibility criteria that can be evaluated based on medical history.
Complete Registry informed consent procedures according to overseeing Institutional Review Board (IRB)/Ethics Committee (EC) requirements.
Obtain ID on study website to be enrolled into initial screening.
Complete the Registry/Screening Visit<ol type="i">
Confirm Registry eligibility criteria
Determine Vision Cohort**
Confirm Genetic Screening Criteria
<u>Complete Registry data collection as part of the Registry/Screening Visit</u>
Participants meeting eligibility criteria to continue will be enrolled into the genetic screening phase
*Genetic testing will not be performed in this study. A prior conclusive genetic test will be assessed for screening analysis.
** Participants in the Younger Age Cohort will not be assigned a Vision Cohort.</td></tr>
</table>

CATEGORY	DESCRIPTION
	2. Genetic Screening Phase o Genetic reports* for participants ***enrolled into the genetic screening phase*** will be uploaded to study website for review and confirmation by Central Genetics Auditor (CGA) as meeting **Genetic Screening Criteria.** o Participants confirmed as meeting those criteria will be considered ***enrolled into the Registry***. **Genetic testing will not be performed in this study. A prior conclusive genetic test will be assessed for screening analysis.* 3. Registry Phase o The flow of participants who are ***enrolled into the Registry*** depends on whether their causal gene is designated as a **Natural History Study (NHS) Target Gene:** ▪ **Not designated as NHS Target Gene:** Annual phone calls up to 48 months from the Registry/Screening Visit or until gene is designated as NHS Target Gene. ▪ **Designated as NHS Target Gene:** Participants will be considered ***pending enrollment into the NHS***. 4. Natural History Study (NHS) Phase o Participants ***pending enrollment into the NHS*** will do the following: i. Return to the clinic for the NHS Enrollment/Baseline Visit 1. Complete NHS informed consent procedures according to overseeing Institutional Review Board (IRB)/Ethics Committee (EC) requirements 2. Confirm NHS eligibility criteria 3. Complete Baseline testing 4. Participants completing these steps will be considered ***enrolled into the NHS*** ii. Return to the clinic for follow-up visits according to Cohort specifications. 1. Participants in the Younger Age Cohort and Vision Cohorts 1 and 2 will return to the clinic at 12, 24, 36 and 48 months from the Baseline Visit date for follow-up visits. 2. Participants in Vision Cohort 3 will have phone calls at 12, 24 and 36 months from the Baseline Visit date, and a study visit at 48 months. iii. After the 48-month follow-up visit, participation in the study will be completed for participants in all cohorts.

Outcomes

Functional Outcomes:

Key Assessments	Test	Equipment	Reading Center	Registry (R) or Natural History Study (NHS)
Visual field sensitivity measured with quantitative topographic analysis (hill of vision [HOV])	Static Perimetry (SP)	Octopus 900 Pro	Yes	R, NHS
Early Treatment of Diabetic Retinopathy Study (ETDRS) / HOTV Best Corrected Visual Acuity (BCVA) letter score	Visual Acuity (VA)	Electronic Visual Acuity (EVA) system or ETDRS/HOTV charts	N/A	R, NHS
Low visual acuity test – for participants unable to see ETDRS letters	Low Visual Acuity	Berkeley Rudimentary Vision Test (BRVT)	N/A	R, NHS
ETDRS/HOTV best corrected low luminance visual acuity letter score	Low Luminance Visual Acuity (LLVA)	Electronic Visual Acuity (EVA) system or ETDRS/HOTV charts	N/A	R, NHS
Mean retinal sensitivity	Fundus guided Microperimetry (MP)	MAIA	Yes	NHS
Contrast sensitivity function	Contrast sensitivity	CSV-1000E chart	N/A	NHS
Retinal function using amplitudes and timing in response to rod- and cone-specific stimuli	Full-field Electroretinogram (ffERG)	Diagnosys Espion	No	NHS
Full-field retinal sensitivity	Full-field stimulus threshold (FST) testing to blue, white, and red stimuli	Diagnosys Espion	No	NHS
Color vision function	Color vision	Lanthony D15	N/A	NHS

Structural Outcomes:

Key Assessments	Test	Equipment	Reading Center	Registry (R) or Natural History Study (NHS)
Ellipsoid zone (EZ) area; outer nuclear layer and ganglion cell layer thicknesses	Spectral Domain Optical Coherence Tomography (SD-OCT)	Heidelberg Spectralis	Yes	R, NHS

	Qualitative and quantitative assessments of autofluorescence pattern	Fundus Autofluorescence (FAF)	Optos	Yes	NHS

Patient Reported Outcomes (PROs) (NHS only):

- Adults 18 years or older at Baseline:
  - Michigan Retinal Degeneration Questionnaire (MRDQ)
  - Patient-Reported Outcomes Measurement Information System (PROMIS®-29)
  - Visual Symptom and Impact Outcomes-Patient Reported Outcome (ViSIO-PRO)
  - Ultra Low Vision-Visual Functioning Questionnaire (ULV-VFQ-50) – *Vision Cohort 3 only*
- Adolescents 12-17 years at Baseline:
  - Visual Symptom and Impact Outcomes-Patient Reported Outcome (ViSIO-PRO)
  - L. V. Prasad-Functional Vision Questionnaire (LVP-FVQ II)
- Children 8-11 years at Baseline:
  - Visual Symptom and Impact Outcomes-Observer Reported Outcome (ViSIO-ObsRO)
  - L. V. Prasad-Functional Vision Questionnaire (LVP-FVQ II)
- Children 4-7 years at Baseline:
  - Visual Symptom and Impact Outcomes-Observer Reported Outcome (ViSIO-ObsRO)

RD Rare Gene List	The **RD Rare Gene List** for the Uni-Rare study (see **Uni-Rare Clinical Site Manual of Procedures**) represents all known genes for which variants may be associated with retinal dystrophy (RD) and have not already been studied in a trial at the time this protocol was finalized.
Population	**Key Eligibility Criteria – Determined at the Registry/Screening Visit** The entire list of eligibility criteria in protocol section 2.4.1 must be reviewed at the Registry/Screening Visit. Participants meeting eligibility criteria will continue to ***enroll into the genetic screening phase.***

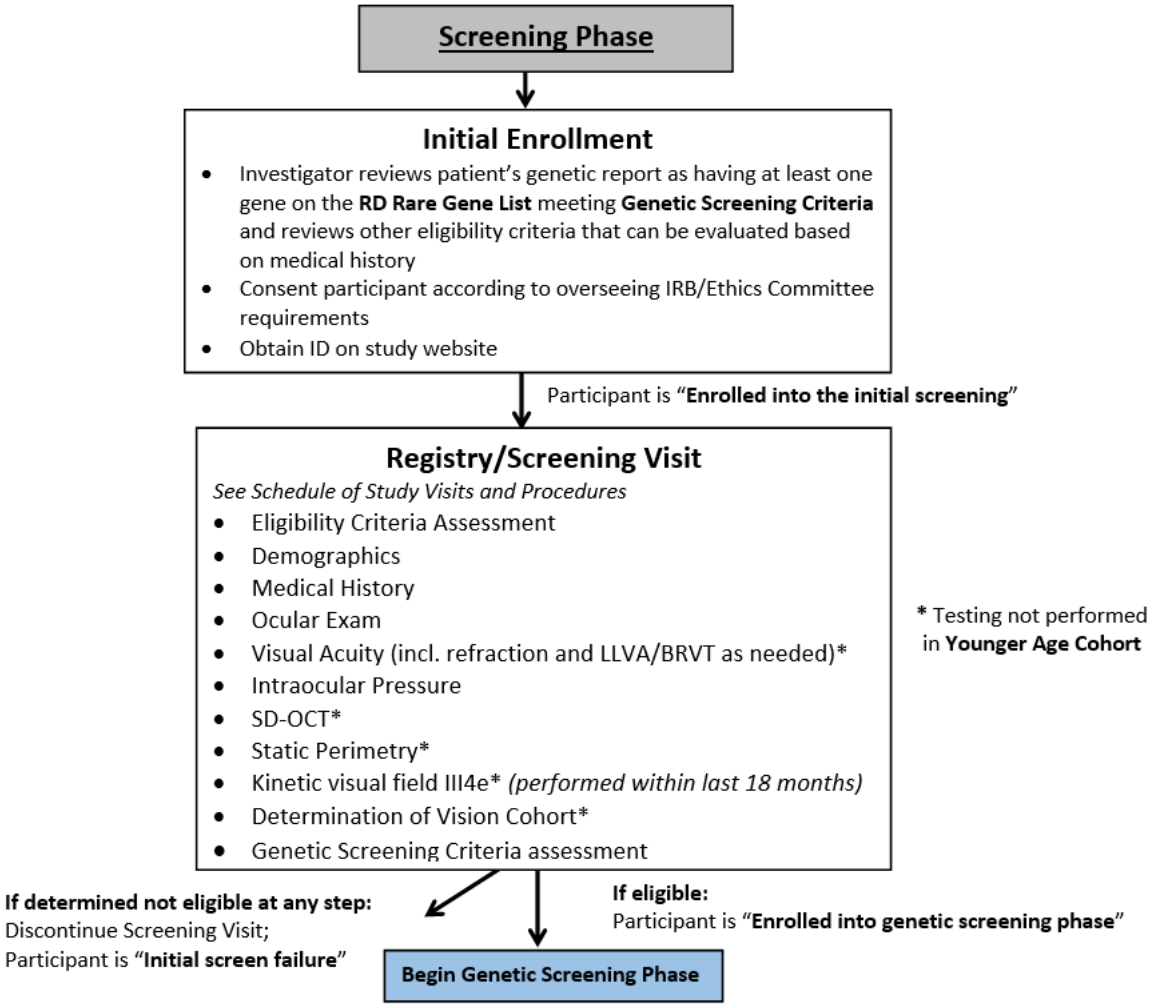
A key subset of the eligibility criteria includes the following:

- Age ≥ 4 years of age
- Clinical diagnosis of retinal dystrophy (RD)
- Must have a gene on the **RD Rare Gene List** which meets one of the following **Genetic Screening Criteria***
  - Inheritance Pattern is Recessive **and** has at least 2 disease-causing variants which are homozygous or heterozygous *in trans*

    OR
  - Inheritance Pattern is Recessive **and** has 2 disease-causing variants with unknown phase **and** meets all the following additional informatic criteria that are consistent with likely segregation *in trans*:
    1. Investigator confirms genotype and phenotype are consistent with autosomal recessive inheritance
    2. The 2 disease-causing variants have **not** been reported *in cis* in variant databases

	3. **No** additional potentially pathogenic variants were found on the gene (and the sequencing data for the gene were sufficiently robust to detect any additional potentially pathogenic variants) 4. **No** potentially pathogenic variants were found in other common, likely candidate genes for the proposed condition **OR** o Inheritance Pattern is Dominant, X-linked, or Mitochondrial **and** has at least 1 disease-causing variant **Based on prior conclusive genetic report from a clinically certified lab (or from a research lab that has been approved by the study Genetics Committee).* **Genetic Screening Phase** The Genetic Screening Phase will confirm genetic cause of disease via final Central Genetics Auditor (CGA) review for all participants. **Registry Cohort Criteria** At the end of the Genetic Screening Phase the following must be documented to be eligible to ***enroll into the Registry***: ➢ Participant's genetic cause of disease has been confirmed by Central Genetics Auditor (CGA) as meeting one of the **Genetic Screening Criteria** for a gene on the **RD Rare Gene List**. **Natural History Study Cohort Criteria** Participants who meet the final ***Registry Cohort Criteria*** will be eligible to enroll into the NHS **if and when their causal gene is designated as an NHS Target Gene**. This gene-by-gene designation will be made by the Executive Committee on an ongoing basis and may depend on funding resources as well as Registry enrollment numbers within gene. NHS consent will be required, and additional NHS eligibility criteria will be confirmed prior to enrollment into the NHS.
Sample Size	**Registry** • Recruitment will continue until 1,500 participants meet the final ***Registry Cohort Criteria***, unless the Executive Committee terminates recruitment due to feasibility. • A maximum of 150 participants in Vision Cohort 3. • A maximum of 100 participants where Inheritance Pattern is Recessive and phase is unknown. • A maximum of 100 participants within gene. The Executive Committee will monitor enrollment distributions across genes, inheritance patterns, vision cohorts, and age cohorts with the planned caps as noted. Enrollment in some genes, inheritance patterns, vision cohorts, or age cohorts may be encouraged to ensure appropriate representation, and some caps may be adjusted if needed. **Natural History Study** • The Natural History Study sample size for each gene will depend on the Registry enrollment; a maximum of 100 participants within gene.

FLOW CHART – SCREENING PHASE



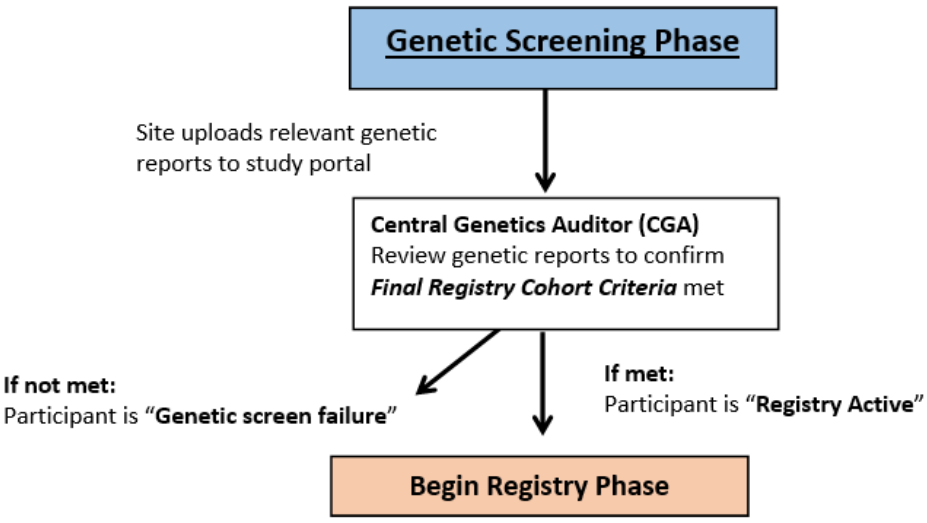
Genetic Screening Criteria

To enter the Genetic Screening Phase, participants must have a gene on the **RD Rare Gene List** meeting one of the following:

Inheritance Pattern[1]	Variant Documentation[2]
Recessive	At least 2 disease-causing variants which are homozygous or heterozygous in trans **OR** 2 disease-causing variants with unknown phase **and** meets all the following additional informatic criteria that is consistent with likely segregation *in trans* ➢ Investigator confirms genotype and phenotype are consistent with autosomal recessive inheritance ➢ The 2 disease-causing variants have **not** been reported *in cis* in variant databases ➢ **No** additional potentially pathogenic variants were found on the gene (and the sequencing data for the gene were sufficiently robust to detect any additional potentially pathogenic variants) ➢ **No** potentially pathogenic variants were found in other common, likely candidate genes for the proposed condition
Dominant, X-linked, or Mitochondrial	At least 1 disease-causing variant

1- Based on protocol-defined **RD Rare Gene List** mapping.
2- Based on prior conclusive genetic report from a clinically certified lab (or from a research lab that has been approved by the study Genetics Committee).

FLOW CHART – GENETIC SCREENING PHASE



Final Registry Cohort Criteria

Participant's genetic cause of disease has been **confirmed by CGA*** as meeting one of the following, for a gene on the **RD Rare Gene List**:

- Inheritance Pattern is Recessive **and** has at least 2 disease-causing variants which are homozygous or heterozygous *in trans*

  OR
- Inheritance Pattern is Recessive **and** has 2 disease-causing variants with unknown phase **and** meets all the following additional informatic criteria that is consistent with likely segregation *in trans*
  - Investigator confirms genotype and phenotype are consistent with autosomal recessive inheritance
  - The 2 disease-causing variants have **not** been reported *in cis* in variant databases
  - **No** additional potentially pathogenic variants were found on the gene (and the sequencing data for the gene were sufficiently robust to detect any additional potentially pathogenic variants)
  - **No** potentially pathogenic variants were found in other common, likely candidate genes for the proposed condition

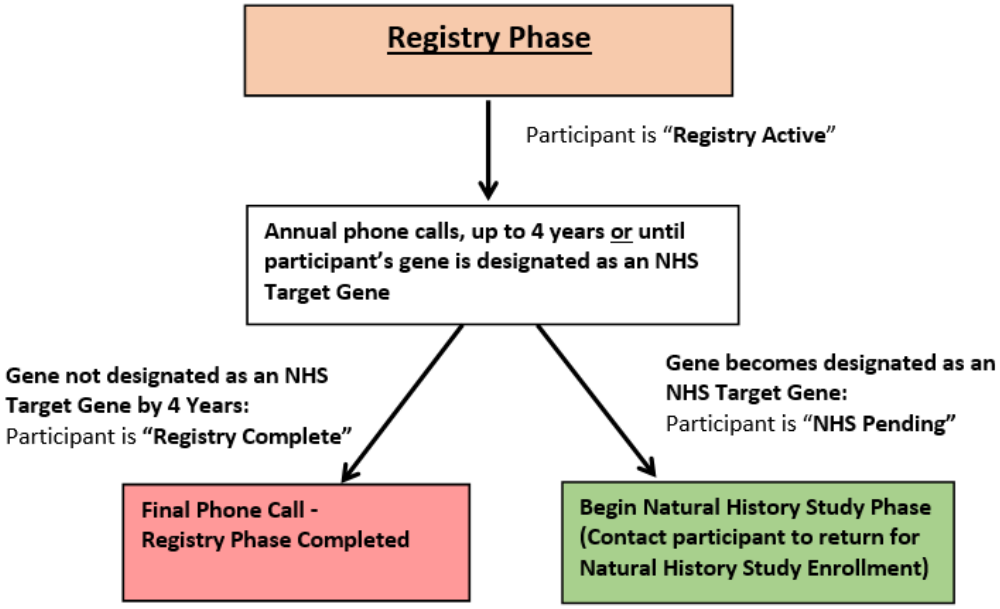
  OR
- Inheritance Pattern is Dominant, X-linked, or Mitochondrial **and** has at least 1 disease-causing variant

**Based on prior conclusive genetic report from a clinically certified lab (or from a research lab that has been approved by the study Genetics Committee).*

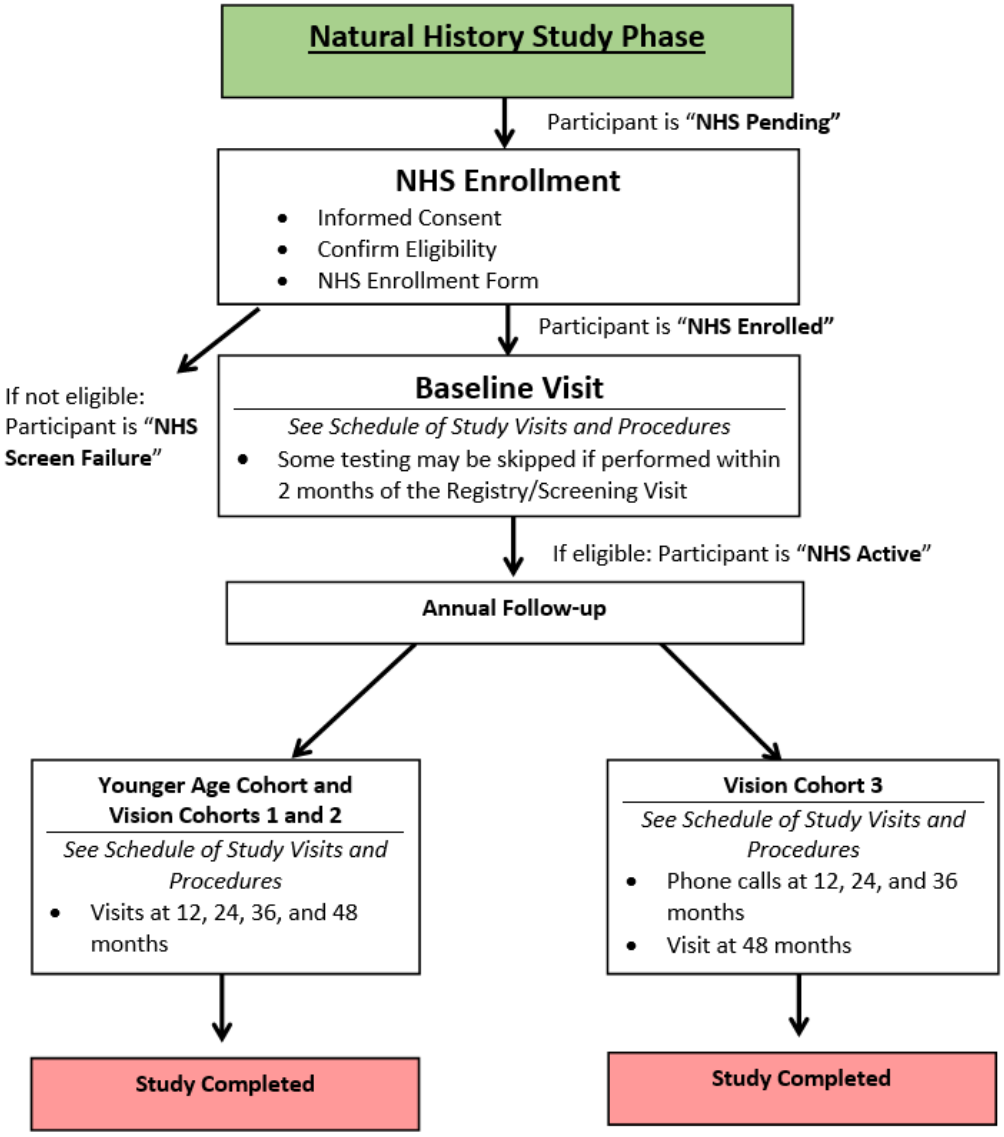
Periodically, all genetic reports of participants enrolled into the final registry cohort will be evaluated by the Genetics Committee for the following. This analysis will not change eligibility to be enrolled into the final registry cohort.

- Interpretation of pathogenicity
- Genetic classifications for analyses

FLOW CHART – REGISTRY PHASE



FLOW CHART – NATURAL HISTORY STUDY



SUMMARY OF PROCEDURES FOR THE REGISTRY/SCREENING VISIT, GENETIC SCREENING PHASE, AND REGISTRY PHASE

Visit/Phase	Registry/ Screening Visit	Genetic Screening Phase	12M	24M	36M	48M
Phone Call Target Windows [a]			Wk 52 ± 8	Wk 104 ± 8	Wk 156 ± 8	Wk 208 ± 8
Participant-Level Procedures						
Registry Informed Consent	X					
Collect MyRetinaTrackerID (if participating and consented to provide)	X					
Eligibility Criteria Assessment	X					
Demographics	X					
Medical History (incl. pre-existing conditions, symptomology history, medications)	X					
Genetic Report Assessment (incl. **Genetic Screening Criteria**)	X					
Determination of **Vision Cohort** [c]	X					
CGA Confirmation of Genetic Cause of Disease and Final Genetic Eligibility		X				
Phone Call (patient contact only; no data collection)			X	X	X	X
Ocular Procedures [b] **–** ***all testing performed in each eye***						
Complete Ophthalmic Exam [d]	X					
Visual Acuity (EVA preferred or ETDRS charts); with refraction and LLVA/BRVT [c]	X					
Intraocular Pressure [e]	X					
SD-OCT Volume Scans [c] (Heidelberg Spectralis)	X					
SD-OCT Vertical and Horizontal Scans [c] (Heidelberg Spectralis)	X					
Static Perimetry [c] (Octopus 900 Pro)	X					
Kinetic VF III4e [c, f] (Kinetic Perimetry)	X					

a. Timed from Registry/Screening Visit; annually up to four (4) years or until participant's gene is designated as an NHS Target Gene.
b. The Registry/Screening Visit date is defined as the start date of all Registry/Screening testing. All Registry/Screening testing must be completed within ninety (90) days of the Registry/Screening Visit date (except for ophthalmic exam and kinetic VF, as noted in d and f below). ***All procedures are considered standard care.***
c. Testing not performed in Younger Age Cohort.
d. Ophthalmic exam can be performed at Registry/Screening Visit, or a historical measurement performed within the last six (6) months prior to the Registry/Screening Visit. The ophthalmic exam includes slit-lamp biomicroscopy and indirect ophthalmoscopy.
e. Intraocular pressure (IOP) measurements are to be taken prior to pupil dilation.
f. **Vision Cohort 1 and 2:** Historical measurement performed ***within the last eighteen (18) months*** prior to the Registry/Screening Visit. If a historical measurement is not available, then perform the Kinetic VF III4e at the Registry/Screening Visit. **Vision Cohort 3:** Collect the ***most recent*** historical measurement prior to the Registry/Screening Visit, if available. Kinetic VF III4e does not need to be performed at screening if a historical measurement is not available.

SCHEDULE OF STUDY VISITS AND PROCEDURES FOR THE NATURAL HISTORY STUDY: YOUNGER AGE COHORT

Visit	**Baseline** [a]	**12M** [b]	**24M** [b]	**36M** [b]	**48M** [b]
Target Windows	(Day 0)	Wk 52 ± 4	Wk 104 ± 4	Wk 156 ± 4	Wk 208 ± 4
Participant-Level Procedures					
NHS Informed Consent	X				
Eligibility Criteria Assessment	X				
Concomitant Medications / Adverse Events / Medical History Update	X	X	X	X	X
Patient Reported Outcomes (PROs)	X		X		X
Ocular Procedures – ***all testing performed in each eye***					
Complete Ophthalmic Exam [c]	X	X	X	X	X
Visual Acuity (HOTV); with refraction and LLVA/BRVT	X	X	X	X	X
Intraocular Pressure [d]	X	X	X	X	X
Color Vision (Lanthony D15)	X	X	X	X	X
SD-OCT Volume Scans (Heidelberg Spectralis [e])	X	X	X	X	X
SD-OCT Vertical and Horizontal Scans (Heidelberg Spectralis [e])	X	X	X	X	X
Axial Length and Corneal Curvature Measurements	X	X	X	X	X
Optos Color Photos [h]	X				
Optos Fundus Autofluorescence [h]	X	X	X	X	X
Full-field ERG (Diagnosys Espion) [f, h]	X				X
Full-field Stimulus Threshold (Diagnosys Espion) [h]	X	X	X	X	X
Age-Up Procedures [g] – ***for participants who turn 8 y/o during study period***					
Static Perimetry (Octopus 900 Pro)		X	X	X	X
Fundus Guided Microperimetry (MAIA) [h]		X	X	X	X
Contrast Sensitivity (CSV-1000E)		X	X	X	X

a. Baseline testing must be started within seven (7) days of NHS eligibility confirmation. The Baseline Visit date is defined as the start date of all Baseline testing. All Baseline testing must be completed within thirty (30) days of the Baseline Visit date, with the following exceptions:
   - If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date for the ophthalmic exam or IOP exam, the testing performed as part of the Registry/Screening Visit for these modalities may be used for the Baseline Visit.
   - PROs may be completed in person or remotely any time within 6 months after Baseline Visit date.

b. All NHS Follow-up Visit testing must be completed on the same day, with the following exception:
   - PROs may be completed in person or remotely any time within the Allowable Window of the associated visit.

c. Ophthalmic exam includes slit-lamp biomicroscopy and indirect ophthalmoscopy. It is recommended that the ocular exam is completed at approximately the same time of day at each visit using the same equipment.

d. Intraocular pressure (IOP) measurements are to be taken prior to pupil dilation.

e. If a Younger Age Cohort participant is unable to perform OCT testing on the Heidelberg Spectralis, the handheld Bioptogen/Envisu may be used to perform OCT testing for qualitative purposes **with approval from the Coordinating Center**.

f. If ERG has been undetectable in the past, there is no need to perform at Baseline Visit; if ERG is undetectable at Baseline Visit, there is no need to perform at 48M - at the investigator's discretion.

g. Participants in the Younger Age Cohort who turn 8 years old (age-up) during the NHS study period should attempt to have static perimetry, microperimetry, and contrast sensitivity testing performed at the next study visit after they turn 8 years old and at every subsequent visit, until the end of the study period.

h. If a site does not have the required equipment, participation in this test may be waived **with approval from the Coordinating Center.**

SCHEDULE OF STUDY VISITS AND PROCEDURES FOR THE NATURAL HISTORY STUDY: VISION COHORTS 1 AND 2

Visit	Baseline [a]	12M [b]	24M [b]	36M [b]	48M [b]
Visit Target Windows	(Day 0)	Wk 52 ± 4	Wk 104± 4	Wk 156± 4	Wk 208± 4
Participant-Level Procedures					
NHS Informed Consent	X				
Eligibility Criteria Assessment	X				
Concomitant Medications / Adverse Events / Medical History Update	X	X	X	X	X
Patient Reported Outcomes (PROs)	X		X		X
Ocular Procedures – *all testing performed in each eye*					
Complete Ophthalmic Exam [c]	X	X	X	X	X
Visual Acuity (EVA preferred or ETDRS charts); with refraction and LLVA/BRVT	X	X	X	X	X
Intraocular Pressure [d]	X	X	X	X	X
Color Vision (Lanthony D15)	X	X	X	X	X
Contrast Sensitivity (CSV-1000E)	X	X	X	X	X
SD-OCT Volume Scans (Heidelberg Spectralis)	X	X	X	X	X
SD-OCT Vertical and Horizontal Scans (Heidelberg Spectralis)	X	X	X	X	X
Axial Length and Corneal Curvature Measurements [e]	X	X	X	X	X
Optos Color Photo [h]	X				
Optos Fundus Autofluorescence [h]	X	X	X	X	X
Full-field ERG (Diagnosys Espion) [f, h]	X				X
Full-field Stimulus Threshold (Diagnosys Espion) [h]	X	X	X	X	X
Static Perimetry (Octopus 900 Pro) [g]	X	X	X	X	X
Fundus Guided Microperimetry (MAIA) [g, h]	X	X	X	X	X

a. Baseline testing must be started within seven (7) days of eligibility confirmation. Baseline Visit date is defined as the start date of all Baseline testing. All Baseline testing must be completed within thirty (30) days of the Baseline Visit date, with the following exceptions:
   - If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date for the visual acuity (VA), static perimetry, SD-OCT (volume and V/H), ophthalmic exam or IOP exams, the testing performed as part of the Registry/Screening Visit may be used for the Baseline Visit. ***A second static perimetry test would still need to be performed at the Baseline Visit, as noted in h below.***
   - PROs may be completed in person or remotely any time within 6 months after Baseline Visit date.

b. All NHS Follow-up Visit testing must be completed on the same day, with the following exception:
   - PROs may be completed in person or remotely any time within the Allowable Window of the associated visit.

c. Ophthalmic exam includes slit-lamp biomicroscopy and indirect ophthalmoscopy. It is recommended that the ocular exam be completed at approximately the same time of day at each visit using the same equipment.

d. Intraocular pressure (IOP) measurements are to be taken prior to pupil dilation.

e. Axial length and corneal curvature measurements will be completed at the Baseline Visit for all participants. Only individuals who are under 18 years old at the Baseline Visit will continue to have measurements taken at every annual visit until study completion.

f. If ERG has been undetectable in the past, there is no need to perform at Baseline Visit; if ERG is undetectable at Baseline Visit, there is no need to perform at 48M - at the investigator's discretion.

g. For static perimetry and microperimetry, all participants will complete two tests for the Baseline Visit. The results will be compared according to the visual field criteria in section 4.3.2 to determine if a third test is needed.
h. If a site does not have the required equipment, participation in this test may be waived **with approval from the Coordinating Center**.

SCHEDULE OF STUDY VISITS AND PROCEDURES FOR THE NATURAL HISTORY STUDY: VISION COHORT 3

Visit	Baseline [a]	12M	24M	36M	48M [b]
Target Windows	(Day 0)	Wk 52 ± 4 (Phone call only)	Wk 104± 4 (Phone call only)	Wk 156± 4 (Phone call only)	Wk 208± 4
Participant-Level Procedures					
NHS Informed Consent	X				
Eligibility Criteria Assessment	X				
Concomitant Medications / Adverse Events / Medical History Update	X	X	X	X	X
Patient Reported Outcomes (PROs)	X				X
Ocular Procedures – *all testing performed in each eye*					
Complete Ophthalmic Exam [c]	X				X
Visual Acuity (EVA preferred or ETDRS charts); with refraction and LLVA/BRVT	X				X
Intraocular Pressure [d]	X				X
SD-OCT Volume Scans (Heidelberg Spectralis)	X				X
SD-OCT Vertical and Horizontal Scans (Heidelberg Spectralis)	X				X
Axial Length and Corneal Curvature Measurements [e]	X				X
Optos Color Photos [f]	X				
Optos Fundus Autofluorescence [f]	X				X
Full-field Stimulus Threshold (Diagnosys Espion) [f]	X				X

a. Baseline testing must be started within seven (7) days of eligibility confirmation. Baseline Visit date is defined as the start date of all Baseline testing. All Baseline testing must be completed within thirty (30) days of the Baseline Visit date, with the following exceptions:
   - If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date for the visual acuity (VA), SD-OCT (volume and V/H), ophthalmic exam or IOP exams, the testing performed as part of the Registry/Screening Visit may be used for the Baseline Visit.
   - PROs may be completed in person or remotely any time within 6 months after Baseline Visit date.

b. All NHS Follow-up Visit testing must be completed on the same day, with the following exception:
   - PROs may be completed in person or remotely any time within the Allowable Window of the associated visit.

c. Ophthalmic exam includes slit-lamp biomicroscopy and indirect ophthalmoscopy. It is recommended that the ocular exam is completed at approximately the same time of day at each visit using the same equipment.

d. Intraocular pressure (IOP) measurements are to be taken prior to pupil dilation.

e. Axial length and corneal curvature measurements will be completed at the Baseline Visit for all participants. Only individuals who were under 18 years old at the Baseline Visit will also have measurements taken at the 48M visit.

f. If a site does not have the required equipment, participation in this test may be waived **with approval from the Coordinating Center**

Chapter 1: Background Information

1.1 Introduction

Inherited retinal degenerations (IRDs) affect approximately 2 to 3 million people worldwide.[1] The rise of promising treatment approaches has increased rapidly in recent years, include gene editing and augmentation (early-stage disease), neuroprotection (mid-stage disease), prosthetics, optogenetics, and cell therapy to restore some light sensation (late-stage disease).[1,2] Despite advancements in therapy development, and a growing number of interventional trials (https://www.clinicaltrials.gov/) for IRDs, there remain significant hurdles to designing trials and moving therapy through the development process. Several papers have reviewed unmet needs and identified top priorities to move the promise of treatment forward amongst a complex landscape of IRD research.[3-7] The common theme among the recommendations is the vital need for natural history studies, the foundational basis for trial design and drug development. The following sections summarize the key gaps in IRD research that natural history studies can address.

1.1.1 Identifying Optimal IRD Patient Populations for Target Therapies

IRDs are genetically diverse (280 causative genes have been identified to date) (https://sph.uth.edu/retnet/) and have vastly different clinical manifestations, including age of onset, severity of disease, rate of progression, and structural and functional abnormalities. Understanding this phenotypic heterogeneity is a major challenge for potential therapy developers. It is critical to identify genetic factors impacting disease severity and progression, including the impact of mutation-specific variations within genes. Natural history data, both longitudinal and cross-sectional, within each gene population is needed to understand these differences, and ideally these studies would include enough cases to evaluate a variety of subgroups across genetic, phenotypic, and environmental factors.[3-7]

1.1.2 Develop and Validate Outcome Measures for Progression of IRDs

The cornerstone of good trial design is a good endpoint. Identifying the best candidate endpoint for evaluating progression of disease, and ultimately treatment effects in a trial, requires consideration of many properties. These include sensitivity, reproducibility, correlation with other measures of disease progression, how much within-person change is beyond measurement variability, and whether within-person change is clinically meaningful. For a given treatment, the best measure also depends on the expected benefit; restoration of vision versus slowing of progression. Since IRDs are genetically diverse, understanding these properties within each gene is important.[3-7]

The list of candidate endpoints to measure and understand IRD progression is vast. **Visual function outcomes,** such as visual acuity (VA), contrast sensitivity, color vision, microperimetry (MP), full-field stimulus threshold (FST) and full-field electroretinogram (ffERG), measure performance of the components of the visual system in the clinical environment and represent the measures of what is clinically meaningful. **Structural or anatomical measures**, such as fundus autofluorescence (FAF) and optical coherence tomography (OCT), represent candidate biomarkers or surrogate endpoints that hold the potential to predict clinical benefit. Structural measures are an expanding area of IRD research due to new technologies and better imaging

acquisition and interpretation techniques and is an area of priority identified by gap analyses. **Functional vision measures**, which are designed to reflect real-life challenges in daily activities, include patient-reported outcomes. Although a variety of tools exist, little is known about their applicability within each genotype.[3-7]

A relatively small number of endpoints defined by these measures have been accepted by the Food and Drug Administration (FDA) and other regulatory bodies to study therapeutic efficacy in IRD trials. The extreme genetic heterogeneity of IRDs and diversity of resulting disease progression further complicates the decision of which endpoint to use for a given gene therapy trial. Gene-specific natural history studies can provide longitudinal data to understand the properties of these measures and facilitate development of appropriate endpoints for trial design.

1.1.3 Other Gaps Addressed by Natural History Studies

Natural history studies address numerous other challenges faced in clinical trial design and implementation, including understanding the time course of disease progression (which informs trial duration and testing schedule), evaluating demographic and epidemiological estimates of prevalence and disease characteristics (which may be addressed by cross-sectional studies), and identifying expert clinical centers with staff trained to follow standardized protocols. They also shed light on intangibles and unknowns, which ultimately saves resources, increases efficiencies, and improves quality of future interventional trials built upon these lessons learned.

1.1.4 Unique Challenges in Ultra-Rare Genes

Ultra-rare genes present a special challenge in addressing these knowledge gaps and represent a significant portion of IRD genes. Two hundred and forty-eight (248) genes out of three hundred and seventy-four (374) potential IRD genes listed in the FFB Consortium 2021 Gene Poll had less than twenty (20) patients counted as having retinal dystrophy (RD) linked to that causal gene, across all thirty-two (32) sites reporting in the Poll (data not published). Small sample sizes create less precision around estimates and difficulty or inability to evaluate factors related to disease severity and progression or correlation among outcomes. Further study is needed to identify similar disease mechanisms and whether there are methods by which researchers could pool data across genes for these objectives.

1.2 Rationale for a Universal Rare Gene Study

Individual natural history studies for each rare RD gene are not feasible. Many centers have as few as one (1) – two (2) patients for a particular RD gene and may not be able to devote resources needed to implement each study. Individual studies also require considerable startup time (e.g., contracts, IRB/Ethics Committee approvals) and study management expenses regardless of the number of patients. A single, universal protocol under which all rare RD genes may be enrolled would address these inefficiencies.

Because of the vast phenotypic diversity, simultaneous open enrollment of all rare RD genes directly into a longitudinal natural history study is problematic. Unfocused enrollment efforts spread across hundreds of genes will dilute timelines for data collection and analysis objectives within targeted genes. A solution is to create a universal registry open to all rare RD genes, to cross-sectionally characterize patients within all rare RD genes (mild, moderate, and severe vision loss) so they are ready to be enrolled into a subsequent universal longitudinal natural

history study as their gene is selected. This two-phase platform will (1) eliminate repetitive processes like certification, training, regulatory approval, contract agreements, (2) reduce costs and accelerate timelines for longitudinal studies and (3) leverage a large sample size and standardized data collection in the cross-sectional study to explore the extent to which genes with common mechanisms of disease have similar clinical manifestations (e.g., determine if and how some genes may be pooled in some analyses).

1.3 Study Objectives

Registry Objectives

1. **Genotype Characterization**
    a. Establish a database of patients completing a standardized genetic screening process confirming retinal dystrophy is associated with disease-causing genetic variants (and thereby confirmed genetically eligible for a potential **natural history study)**
    b. Evaluate characteristics of genetic variants
2. **Cross-Sectional Phenotype Characterization***
    a. Characterize cross-sectional retinal dystrophy associated with disease-causing genetic variants using functional and structural measures, within gene
        i. Ideally where within-gene sample size is 20 or more
    b. Structure-function relationships will also be explored within-gene
        i. Ideally where within-gene sample size is 20 or more
    c. Risk factors for disease severity will also be explored within-gene
        i. Ideally where within-gene sample size is 40 or more
3. **Establish a Link to My Retina Tracker Registry (MRTR)**
    a. Register MRTR participants for exploratory analysis of data between registry databases, as permissible within the scope of signed informed consent(s)
4. **Ancillary Exploratory Studies - Pooling of Genes**
    a. Explore whether phenotype-genotype associations within biological mechanisms or other factors (such as age or disease duration) will allow pooling of genes for cross-sectional analysis objectives
    b. If pooling is determined appropriate, evaluate objective 2 above within appropriate pooling groups

Natural History Study Objectives

Within-Gene Objectives*

The following objectives will be evaluated within gene.

1. **Natural History**
    a. Characterize the natural history of retinal degeneration associated with disease-causing genetic variants over 4 years, using functional, structural, and patient-reported outcome measures
    b. Ideally where within-gene sample size is 20 or more
2. **Structure-Function Relationship**
    a. Explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with disease-causing genetic variants
    b. Ideally where within-gene sample size is 20 or more

3. **Risk Factors for Progression**
    a. Explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with disease-causing genetic variants
    b. Ideally where within-gene sample size is 40 or more

*Applicability of within-gene objectives will depend on within-gene sample size as noted above. If less than 20, the primary objective will be limited to describing the cohort in the form of case histories. Objectives may still be explored depending on the needs of a specific gene.

Across-Genes Objective

The following objective will be evaluated across genes.

4. **Ancillary Exploratory Studies - Pooling of Genes**
    a. Explore whether phenotype-genotype associations within biological mechanisms or other factors (such as age or disease duration) will allow pooling of genes for longitudinal analysis objectives

1.4 Potential Risks and Benefits

1.4.1 Known Potential Risks

Most examination procedures are considered part of standard care for retinal degenerations. This study will be capturing some information about participants that include identifiable, personal information, like date of birth (will be collected if permitted by site's regulatory bodies). The study has procedures in place to protect that information. However, there is a chance that a loss of that protection could occur. This would be a loss of confidentiality. There are special efforts being made to ensure that this does not happen.

The sections below summarize the risks and discomforts that may be occur during the period of prospective data collection.

- Risks associated with testing VA, KP, SP, MP, FST, ERG, OCT, and PROs may include boredom and frustration, but no lasting adverse effects are associated with these noninvasive tests
- Dilating eye drops will be used as part of the ophthalmic examination and before some tests. Dilating eye drops may sting, cause light-sensitivity, or an allergic reaction. There is a small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. However, all participants will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small. If glaucoma occurs, treatment is available.
- In rare instances, the cornea may be scratched during measurement of IOP or use of a contact lens electrode. An abrasion like this may be painful, but it heals quickly with no lasting effects. If a participant experiences a corneal abrasion, a tear ointment may be administered, and an eye patch or gauze may be placed over the eye.

1.4.2 Known Potential Benefits

Study participants are not expected to benefit directly from participation in this study. Study participants participating in this study may benefit from close attention from the study personnel

and Investigator(s). The risks of participating in the study are outweighed by the benefits. Benefits include increased attention from the study personnel and the ability to contribute to increased understanding of the cross-sectional description and natural history of retinal degenerations due variants in rare genes, which may contribute to future development of treatments.

1.4.3 Risk Assessment

The risk level for this protocol is considered no greater than minimal risk. A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

1.5 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Employing a cross-sectional registry component combined with the Natural History Study prospective longitudinal study design is advantageous because it reflects a systematic method of data collection. By doing so, this study addresses the need to evaluate disease progression while also accounting for prevalence and disease characteristics. This study design incorporates several strategies to minimize bias, detailed below, using considerations from "Rare Diseases: Natural History Studies for Drug Development: Guidance for Industry, Draft Guidance.[8] These are considered standard for treatment trials and will enhance the translation of the data from this study to a treatment trial.

Establishing standardized testing procedures and specific required equipment for all investigators, leading to greater consistency and precision in the information collected.

Training and certification of study staff who will perform primary outcome procedures by a Reading Center. The Reading Center will grade test results in a uniform manner independently from study sites.

Use of standard, consistent definitions of pre-existing medical conditions, medications and treatments, and adverse events (AEs) across all clinical sites.

A consistent schedule of follow-up visits for all participants with established visit time frames.

A coordinating center (CC) is responsible for monitoring the conduct of the study to ensure adherence to protocol.

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data.

Chapter 2: Registry Enrollment and Registry/Screening Visit

2.1 Registry Recruitment and Enrollment

Registry participants will be recruited from approximately forty (40) clinical sites worldwide. All eligible participants will be included without regard to gender, race, or ethnicity. The primary recruitment strategy will be patient referral from the site Investigator(s). However, recruitment materials may be made used upon IRB or Ethics Committee approval.

The Executive Committee will review recruitment progress and feasibility at regular intervals. **Registry recruitment will continue until approximately 1,500 participants meet the final *Registry Cohort Criteria*** (see section 2.6), unless the Executive Committee terminates recruitment due to feasibility. The Executive Committee will monitor enrollment distributions across genes, inheritance patterns, vision cohorts, and age cohorts with the planned caps as noted below. Enrollment in some genes, inheritance patterns, vision cohorts, or age cohorts may be encouraged to ensure appropriate representation, and some caps may be adjusted if needed.

- A **maximum of 100** participants will be enrolled within gene.
- Recruitment will be tracked within the three (3) vision cohorts as defined below:
  - A **maximum of 150** participants will be enrolled in Vision Cohort 3 (across genes).
  - Approximate target distribution of Vision Cohort 1 and 2 is 2:1 overall and within gene. This will be monitored and encouraged, but not required.
- A **maximum of 100** participants will be enrolled where Inheritance Pattern is Recessive and phase is unknown.
- Participants will *not* be counted as ***enrolled into the Registry*** until **Genetic Screening Criteria** have been confirmed (see section 2.5). This means that potentially more participants will complete the Registry/Screening Visit than are ***enrolled into the Registry***. The number and reasons for screen failures will be tracked. It is possible that some participants will have completed the Registry/Screening Visit and will be awaiting genetic confirmation at the time the enrolled numbers reach the limits above. Therefore, the actual enrolled numbers may be larger. To limit over-enrollment, clinical sites will be notified as the recruitment limits are reached and efforts will be made to accurately predict numbers in the genetic screening queue.

2.2 Cohort Definitions

Vision Cohort Definitions

Vision Cohort 1 Approximately **900** participants	Criteria that must be met in the **better eye*** at the Registry/Screening Visit: ○ **visual acuity** ETDRS letter score of 54 or more (approximate Snellen equivalent 20/80 or better) **and visual field**** diameter 10 degrees or more in every meridian of the central field
Vision Cohort 2 Approximately **450** participants	Criteria that must be met in the **better eye*** at the Registry/Screening Visit: ○ **visual acuity** ETDRS letter score of 19-53 (approximate Snellen equivalent 20/100 to 20/400) **OR**

	○ **visual acuity** ETDRS letter score of 54 or more (approximate Snellen equivalent 20/80 or better) **and visual field**** diameter less than 10 degrees in any meridian of the central field
Vision Cohort 3 Approximately **150** participants	Criteria that must be met in the **better eye*** at the Registry/Screening Visit: ○ **visual acuity** ETDRS letter score of 18 or less (approximate Snellen equivalent 20/500 or worse)
***Better Eye**	The **better eye** is defined as the eye with the better Registry/Screening Visit ETDRS visual acuity. However, if both eyes have the same visual acuity, which is defined as the same Snellen equivalent, then the determination will be made at the Investigator's discretion. In this scenario, the Investigator will consider the eye with better fixation or clearer ocular media to permit highest quality retinal imaging.
****Visual Field**	The **visual field** (VF) is defined as the clinically determined **kinetic VF III4e** performed within the last 18 months prior to the Registry/Screening Visit or performed on the day of the Registry/Screening Visit.

Vision Cohort Grid

	VF diameter ≥10° in every meridian	VF diameter <10° in any meridian
20/80 or better	Vision Cohort 1	Vision Cohort 2
20/100-20/400	Vision Cohort 2	Vision Cohort 2
20/500 or worse	Vision Cohort 3	Vision Cohort 3

Younger Age Cohort Definition

Younger Age Cohort	• Participants who are between the ages of ≥ 4 years and < 8 years old will be designated as the Younger Age Cohort. • Participants in this cohort will not be assigned a Vision Cohort. • Registry/Screening Visit and Natural History Study Visits will have an abbreviated testing schedule.

2.3 Registry Informed Consent and Authorization Procedures

There will be two separate consent processes for the two phases of the Uni-Rare study. There will be one (1) consent process for the Registry phase and one (1) for the NHS phase. The Registry consent process is as follows. Some sites outside the US may have alternative or additional Ethics Committee requirements, which will be followed as applicable, once reviewed and approved by the FFB Consortium.

- Registry Consent Process for Age of Majority: For study participants who are the age of majority, e.g., at least eighteen (18) years of age in the US, the study will be discussed with the potential study participant by trained and delegated study staff. The potential

study participant will be given the current, approved Registry Informed Consent Form (ICF) to read and will be given the opportunity to ask questions about the Registry. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study. If the person wishes to be a participant, then the Registry ICF will be signed/dated and a signed/dated copy of the Registry ICF will be provided to the participant and another copy will be added to the participant's study record.

- Registry Consent Process for Minors: For potential participants who are minors, e.g., under eighteen (18) years of age in the US, a parent/legal guardian (referred to subsequently as "parent") will be provided with the Registry Informed Consent Form (ICF) to read and will be given the opportunity to ask questions about the Registry. If the parent agrees to participate, the Registry ICF will be signed/dated by the parent. The signed/dated Registry ICF will be provided to the parent and another copy will be added to the participant's study record. Participants who become age of majority, e.g., eighteen (18) years of age in the US, while in the Registry will need to re-consent with a Registry ICF (and authorization as described below), as applicable to the IRB or Ethics Committee requirements and as instructed by the FFB Consortium.

  Note: Some Ethics Committees might require a separate Registry Assent for minors who are participating in the Registry, in addition to the Registry ICF signed by the parent/legal guardian. Such applicable requirements will be followed as instructed by the FFB Consortium.

- Authorization for Use/Release of Personal Information: As part of the informed consent process, each participant and/or parent will be asked to sign/date an authorization for release of personal information (or other such document, e.g., HIPAA Authorization, GDPR Consent, LGPD Consent, etc.), as applicable to the IRB or Ethics Committee requirements. The trained and delegated study staff will review the study-specific information that will be collected and to whom that information will be disclosed. While speaking with the participant, questions will be answered about the details regarding authorization. If they wish to proceed, then they will receive a copy of the signed/dated authorization and another copy will be filed in the participant's study record.

- Other Consent Options:

  - Short Form: If a participant or parent prefers that the study information be presented verbally/orally (e.g., they have significant visual impairments), a short form version of the Informed Consent Form, with the corresponding short form summary, may be used as approved by the IRB or Ethics Committee requirements and as instructed by the FFB Consortium.

    - ***Note:*** *This process does require a witness. This process is not to be used as a substitute for presenting study information to the participant either due to written material not being translated in the native language of the participant/LAR or because a participant lacks the capacity to consent.*

  - Remote Consent: At the discretion of the site, as applicable to the IRB or Ethics Committee requirements, and with the approval of the FFB Consortium, some participants may complete the consent process remotely.

- ***Note:*** *This process typically requires additional documentation regarding the remote consent process (e.g., remote consent checklist).*

- Completion of Consent Process and Enrollment: A participant is considered ***enrolled into initial screening*** when the Registry informed consent process has been completed and a participant ID has been obtained on the study website.

2.4 Registry/Screening Visit

After the informed consent documents have been signed, the participant will be evaluated for study eligibility through the elicitation of a medical history and performance of ophthalmic tests as described below. The Registry/Screening Visit date will be documented as the date Registry/Screening procedures begin. All Registry/Screening Visit testing procedures must be completed within ninety (90) days of the Registry/Screening Visit date, unless specified below.

2.4.1 Registry Eligibility Criteria

To be eligible to ***enroll into the genetic screening phase,*** a study participant must meet all the inclusion criteria and none of the exclusion criteria at the Registry/Screening Visit.

2.4.1.1 Participant Inclusion Criteria

Participants must meet all the following inclusion criteria at the Registry/Screening Visit to be eligible to ***enroll into the genetic screening phase***:

1. Willing to participate in the study and able to communicate consent during the consent process
2. Willing and able to complete all applicable **Registry/Screening Visit** assessments
3. Age ≥ 4 years
4. Must have a single gene on the **RD Rare Gene List** which meets one of the **Genetic Screening Criteria** below based on a genetic report* from a clinically certified lab (or from a research lab which has been approved by the study Genetics Committee):
    - Inheritance Pattern is Recessive **and** has at least 2 disease-causing variants which are homozygous or heterozygous *in trans*

      OR
    - Inheritance Pattern is Recessive **and** has 2 disease-causing variants with unknown phase **and** meets all the following additional informatic criteria that is consistent with likely segregation *in trans*:
        1. Investigator confirms genotype and phenotype are consistent with autosomal recessive inheritance
        2. The 2 disease-causing variants have **not** been reported *in cis* in variant databases
        3. **No** additional potentially pathogenic variants were found on the gene (and the sequencing data for the gene were sufficiently robust to detect any additional potentially pathogenic variants)
        4. **No** potentially pathogenic variants were found in other common, likely candidate genes for the proposed condition

      OR

- Inheritance Pattern is Dominant, X-linked, or Mitochondrial **and** has at least 1 disease-causing variant

Important Note:

- ***Genes Listed as Variable Mode of Inheritance on RD Rare Gene List***
  - If the site is able to determine the inheritance pattern from the participant's genetic report*, the **Genetic Screening Criteria** above may be followed to determine eligibility based on the site determined inheritance pattern.
  - If the site is unable to determine the inheritance pattern from the participant's genetic report*, the site should use the most common inheritance pattern to follow the **Genetic Screening Criteria** above. The most common inheritance pattern will be provided to sites for each gene that is listed as having a variable mode of inheritance.
- If there are questions about interpretations of the genetic reports* prior to the genetic screening phase, the Genetics Committee (GC) and/or the Central Genetics Auditor (CGA) may be consulted. The Coordinating Center (CC) must be contacted first to determine the appropriate mechanism of consultation, consistent with regulatory and consent requirements.

**Genetic testing will not be performed in this study. A prior conclusive genetic test is what will be assessed for screening analysis.*

2.4.1.2 Ocular Inclusion Criteria

Both eyes must meet the following criteria at the Registry/Screening Visit to ***enroll into the genetic screening phase***.

1. Both eyes must have a clinical diagnosis of retinal dystrophy
2. Both eyes must permit good quality photographic imaging (e.g., but not limited to, clear ocular media, adequate pupil dilation, stable fixation)

2.4.1.3 Participant Exclusion Criteria

Participants must not meet any of the following exclusion criteria at the Registry/Screening Visit to be eligible to ***enroll into the genetic screening phase***.

1. History of more than 1 year of cumulative treatment, at any time, with an agent associated with pigmentary retinopathy including amiodarone, chloroquine, deferoxamine, hydroxychloroquine, pentosan polysulfate, tamoxifen, and deferoxamine

Note: Since this is an observational study, pregnant women will not be specifically excluded from participation. **However, minors that are pregnant shall be precluded from participation until they become the age of majority.**

2.4.1.4 Ocular Exclusion Criteria

If either eye has any of the following ocular exclusion criteria at the Registry/Screening Visit, then the participant is not eligible to ***enroll into the genetic screening phase***.

1. Current vitreous hemorrhage
2. Current complications of pathological myopia (for example, but not limited to, myopic maculopathy including atrophy, scar, choroidal neovascularization, schisis) that could inhibit ability to obtain good quality photographic imaging

3. History of intraocular surgery (for example, but not limited to, cataract surgery, vitrectomy, penetrating keratoplasty, or LASIK) within 3 months of Registry/Screening Visit
4. Current or any history of confirmed diagnosis of glaucoma (for example, but not limited to, glaucomatous VF changes or nerve changes, or history of glaucoma filtering surgery)
5. Current or any history of retinal vascular occlusion or proliferative diabetic retinopathy
6. History or current evidence of ocular disease that, in the opinion of the Investigator, may confound assessment of visual function (for example, but not limited to, tractional or rhegmatogenous retinal detachment, any vitreoretinal surgery, retinal vascular occlusion, proliferative diabetic retinopathy)
7. The following medications and treatments are prohibited as they can affect progression of retinitis pigmentosa (RP). The participant must not have received the following treatments:
   - Any use of ocular stem cell or gene therapy
   - Any treatment with ocriplasmin
   - Treatment with Ozurdex (dexamethasone), Iluvien, or Yutiq (fluocinolone acetonide) intravitreal implant
8. The following medications and treatments are excluded **within the specified timeframe**:
   - Treatment with an ophthalmic oligonucleotide **within the last 9 months** (last treatment date is less than 9 months prior to Registry/Screening Visit date)
   - Treatment with any other product **within five times the expected half-life** of the product (time from last treatment date to Registry/Screening Visit date is at least 5 times the half-life of the given product)

2.4.2 Registry/Screening Visit Data Collection and Testing

The following procedures will be performed at the Registry/Screening Visit. An overview of the equipment and certification requirements for all testing is in section 6.1. All Registry/Screening Visit testing procedures must be completed within ninety (90) days of the Registry/Screening Visit date, unless specified below. All ocular testing will be performed in each eye, right eye (OD) first and then left eye (OS). Screening procedures will last approximately two (2) hours. The testing procedures are detailed in the **Uni-Rare Clinical Site Manual of Procedures**.

All Registry/Screening Visit testing procedures are considered standard care.

The following procedures will be performed and documented (including data collection and eligibility criteria checks) at the Registry/Screening Visit:

1. Inclusion and exclusion criteria assessed
2. Demographics (date of birth, sex, race, and ethnicity)
3. Contact information (retained at the site and not entered on the study database)
4. Collection of MyRetinaTracker Registry ID (if participating and consented to provide)
5. Medical history – will be elicited from the study participant and extracted from available medical records, including patient-reported daily activities, pre-existing medical conditions, medications, and audiology history

6. Concomitant medications
7. Ophthalmic examination
    - Can be performed within ninety (90) days of the Registry/Screening Visit or a historical measurement performed ***within the last six (6) months*** prior to the Registry/Screening Visit.
    - Complete ophthalmic examination to include:
        - Slit lamp biomicroscopy
        - Indirect ophthalmoscopy
8. Visual acuity (including refraction, ETDRS, BRVT if needed, and LLVA if needed)*
    - The VA letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.
9. Intraocular Pressure (IOP)
    - IOP measurements are to be taken prior to pupil dilation.
10. Spectral Domain Optical Coherence Tomography (SD-OCT)*
    - Volume Scan
    - Vertical and Horizontal Scan
11. Static Perimetry (SP)*
12. Kinetic Visual Field III4e (Kinetic Perimetry [KP])*
    - **Vision Cohort 1 and 2:** Historical measurement performed ***within the last eighteen (18) months*** prior to the Registry/Screening Visit. If a historical measurement is not available, then perform the Kinetic VF III4e during the Registry/Screening Visit.
    - **Vision Cohort 3:** Collect the ***most recent*** historical measurement prior to the Registry/Screening Visit, if available. Kinetic VF III4e does not need to be performed at screening if a historical measurement is not available.
13. Determination of Vision Cohort (see section 2.2)
    - If the participant's determined Vision Cohort is closed for enrollment, the remainder of procedures and testing are not required. Participant will be discontinued as an ***initial screen failure***.
    - Participants in the Younger Age Cohort will not be assigned to a Vision Cohort.
14. Genetic screening assessment, including number and phase of mutations in the causal gene, history of consanguinity, and collection of the source genetic report(s) available at the clinical site.
    - This includes an assessment that the participant meets one of the **Genetic Screening Criteria**. If the participant does not meet one of these criteria, then the remainder of procedures and testing are not required. The participant will be discontinued as an ***initial screen failure***.

**This testing procedure will not be completed for participants in the Younger Age Cohort.*

2.4.3 Initial Screen Failures

Participants who do not meet criteria to continue as noted above will be discontinued as an ***initial screen failure***. The Screening Visit Form will still be completed, entering "Not Done" for testing not finished. A Final Status Form will be completed, and the reason for screen failure will be noted.

2.5 Genetic Screening Phase

Participants passing the initial screening and ***enrolled into the genetic screening phase*** will have their genetic lab reports submitted for Central Genetics Auditor (CGA) review. The schematic of study design at the beginning of the protocol summarizes the flow of the **Genetic Screening Phase**. Reference the **Uni-Rare Clinical Site Manual of Procedures** for detailed procedures.

All genetic reports will be uploaded to the FFB study website by the clinical site. These reports may be reviewed by the CC, associated clinical site, CGA, Genetics Committee, and Investigator(s) involved in the oversight of the study (which includes the study chair, Operations Committee, and Executive Committee). All genetic reports will be de-identified and redacted of all personal data prior to uploading on the FFB study website.

The CGA will review the genetic documentation provided by the clinical site to verify the genetic screening data entry and appropriate documentation of the **Genetic Screening Criteria.** Additional documentation, including relevant family history information, may be requested as needed to complete this verification process.

- If **Genetic Screening Criteria** are verified, then the participant will be considered ***enrolled into the Registry***.
- If the final study cohort is not verified, then the participant will be a **genetic screen failure**.
    - **NOTE:** Genetic screen failures may include cases where CGA determines the following:
        - More than one gene meets **Genetic Screening Criteria**
        - The actual inheritance pattern, according to CGA review, for the participant differs from the common designation on the **RD Rare Gene List** or identified by the site, and the associated **Genetic Screening Criteria** are no longer met
        - Informatic criteria for Recessive with unknown phase is not confirmed to be consistent with segregation *in trans*
        - Any of the inclusion/exclusion criteria under section 2.4.1 related to genetics are not met

2.5.1 Genetic Screen Failures

Participants who do not meet criteria to continue in the study will be discontinued as a **genetic screen failure**. A Final Status Form will be completed, and the reason for screen failure will be indicated.

2.5.2 Genetics Committee Review

A Genetics Committee (GC) will review the genetic documentation of participants ***enrolled into the Registry*** for interpretation and evaluation of whether the mutations in the affected gene are causative of the disease (for example, pathogenic, likely pathogenic). Cases that are not confirmed as disease causing will remain in the study and will not be considered ineligible. However, their data may be analyzed separately from those with pathogenic mutations.

2.6 Final Registry Cohort Criteria

Participants who meet the **Genetic Screening Criteria** (section 2.4.1.1) and have those criteria confirmed by a CGA will be considered ***enrolled into the Registry.***

Chapter 3: Registry Phase

3.1 Evaluation of Natural History Study (NHS) Target Gene Status

Participants meeting criteria to ***enroll into the Registry*** (section 2.6) will be evaluated for NHS status.

- If the participant's causal gene is designated as an **NHS Target Gene** at the time the CGA confirmation of Genetic Screening Criteria occurs, the participant will be considered ***pending NHS*** and will be asked to return to the clinical site for NHS Enrollment and Baseline Visit (procedures detailed in chapter 4).
- If the participant's causal gene is **not** designated as an **NHS Target Gene** at the time the CGA confirmation of Genetic Screening Criteria occurs, the participant will remain active in the Registry Phase as follows:
  - Participants who are active in the Registry Phase will follow section 3.2 until the end of the Registry Phase of the study or until the participant's causal gene is designated as an **NHS Target Gene.**
  - When the causal gene is designated as an **NHS Target Gene**, the participant will be considered ***pending NHS*** and will be asked to return to the clinical site for NHS Enrollment and Baseline Visit (procedures detailed in chapter 4).

3.2 Annual Phone Calls

The clinical site will call participants who are active in the Registry Phase annually according to the schedule below and will log the phone call on the study website. The purpose of the call is to maintain contact with the participant and update the participant on the status of the study, including any potential for their causal gene to become an NHS Target Gene or potential for interest in other studies.

Schedule for Phone Calls

PHONE CALL SCHEDULE	TARGET DATE*	TARGET WINDOW*	ALLOWABLE WINDOW*
12-Month	52 Weeks	± 8 Weeks	± 26 Weeks
24-Month	104 Weeks	± 8 Weeks	± 26 Weeks
36-Month	156 Weeks	± 8 Weeks	± 26 Weeks
48-Month	208 Weeks	± 8 Weeks	± 26 Weeks

*Timed from Registry/Screening Visit Date

3.3 Completion of Registry Phase

If a participant's causal gene has not been designated as an **NHS Target Gene** by the time of the 48-Month phone call, they will complete the Registry Phase and Uni-Rare study. The participant will be told on the 48-Month phone call that the annual study phone calls will discontinue and their study status will be complete. A Final Status Form will be completed.

Chapter 4: Natural History Study Enrollment and Baseline Visit

4.1 Natural History Study (NHS) Target Gene Selection

The designation of **NHS Target Genes** will be made by the Executive Committee on an ongoing basis and may depend on funding resources as well as Registry enrollment numbers within gene.

The Natural History Study sample size for each gene will depend on Registry enrollment. Since the within-gene Registry limit is 100 participants, this will be the maximum sample size for NHS Target Genes. As noted in section 2.1, the actual enrolled numbers may be larger due to lag in genetic screening phase confirmation of participant meeting the final ***Registry Cohort Criteria***.

Within-gene sample size justification can be derived from the sample size estimates and statistical considerations in chapter 9.

4.2 NHS Enrollment

When a participant's causal gene is designated as an **NHS Target Gene**, the participant will be considered ***pending NHS*** and will be asked to return to the clinical site for NHS Enrollment and the Baseline Visit.

4.2.1 NHS Informed Consent and Authorization Procedures

There will be two separate consent process for the two phases of the Uni-Rare study. There will be one (1) consent process for the Registry phase and one (1) for the NHS phase. The NHS consent process is as follows. Some sites outside the US may have alternative or additional Ethics Committee requirements which will be followed as applicable, once reviewed and approved by the FFB Consortium.

- NHS Consent Process for Age of Majority: For study participants who are the age of majority, e.g., at least eighteen (18) years of age in the US, the study will be discussed with the potential study participant by trained and delegated study staff. The potential study participant will be given the current, approved NHS Informed Consent Form (ICF) to read and will be given the opportunity to ask questions about the NHS. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study. If the person wishes to be a participant, then the NHS ICF will be signed/dated and a signed/dated copy of the NHS ICF will be provided to the participant and another copy will be added to the participant's study record.
- NHS Consent Process for Minors: For potential participants who are minors, e.g., under eighteen (18) years of age in the US, a parent/legal guardian (referred to subsequently as "parent") will be provided with the NHS Informed Consent Form (ICF) to read and will be given the opportunity to ask questions about the NHS. If the parent agrees to participate, the NHS ICF will be signed/dated by the parent. The signed/dated NHS ICF will be provided to the parent and another copy will be added to the participant's study record. Participants who become age of majority, e.g., eighteen (18) years of age in the US, while in the NHS will need to re-consent with an NHS ICF (and authorization as described below), as applicable to the IRB or Ethics Committee requirements and as instructed by the FFB Consortium.

Note: Some Ethics Committees might require a separate NHS Assent for minors who are participating in the Natural History Study, in addition to the NHS ICF signed by the parent/legal guardian. Such applicable requirements will be followed as instructed by the FFB Consortium.

Please reference section 2.3 for details regarding the Authorization for Use/Release of Personal Information, Short Form Option, and Remote Consent Option.

4.2.2 NHS Eligibility Criteria

To be eligible to ***enroll into the NHS,*** a study participant must meet the following criteria:

1. Enrolled into the Registry
    a. Registry eligibility criteria (section 2.4.1) must be reviewed to confirm nothing has changed and criteria are still met
    b. Genetic Screening Criteria do not require a second review
2. Willing to participate in the Natural History Study and able to communicate consent during the consent process
3. Willing and able to complete all Natural History Study visit assessments at each visit over the forty-eight (48) month study period
4. Is <u>not</u> planning or expected to enter experimental treatment trial at any time during the Natural History Study
5. Is <u>not</u> planning to receive any treatments or medications in either eye or systemically that could affect progression of retinitis pigmentosa (RP), including the following:
    - Any use of ocular stem cell or gene therapy
    - Any treatment with ocriplasmin
    - Treatment with Ozurdex (dexamethasone), Iluvien or Yutiq (fluocinolone acetonide) intravitreal implant

A participant is considered ***enrolled into the NHS*** when the required NHS informed consent document(s) have been signed, NHS eligibility criteria are confirmed, and an NHS Enrollment Form is completed on the study website. **This date is considered the NHS Enrollment Date.**

Participants who do not meet criteria to continue as noted above will be discontinued as an ***NHS screen failure***. A Final Status Form will be completed, and the reason for screen failure will be noted.

4.3 Baseline Visit Testing Procedures

The Baseline Visit must begin on or within seven (7) days of NHS Enrollment Date. The Baseline Visit date will be documented as the date Baseline testing procedures begin. All Baseline Visit testing procedures must be completed within thirty (30) days of the Baseline Visit date, unless specified below.

The following procedures will be performed at the Baseline Visit. An overview of the equipment and technician requirements for all testing is in section 6.1. All ocular testing will be performed in each eye, right eye (OD) first and then left eye (OS). Baseline procedures will last

approximately four (4) hours. The testing procedures are detailed in the **Uni-Rare Clinical Site Manual of Procedures**.

4.3.1 Younger Age Cohort

1. Medical updates to include:
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - ViSIO-ObsRO
   - The PROs may be completed in person or remotely (phone or other remote methods) any time within six (6) months of the Baseline Visit (not required to be the same day as the rest of the Baseline Visit).
3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date and the ophthalmic examination was performed during the Registry/Screening Visit (i.e., not historical)– the ophthalmic examination testing procedure may be skipped.***
4. Visual Acuity (including refraction, HOTV, BRVT if needed, LLVA if needed)
   - The visual acuity (VA) Snellen score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.
5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the IOP testing procedure may be skipped.***
6. Color Vision
   - Desaturated (Lanthony D15)
7. Spectral Domain Optical Coherence Tomography (SD-OCT)
   - Volume Scan
   - Vertical and Horizontal Scan
   - If unable to perform OCT testing on the Heidelberg Spectralis, a site may use the handheld Bioptogen/Envisu to perform OCT testing for qualitative purposes **with approval from the Coordinating Center**.
8. Axial Length and Corneal Curvature Measurements

9. Optos Color Photos*
10. Optos Fundus Autofluorescence (FAF)*
11. Full-field Electroretinogram (ffERG)*
12. Full-field Stimulus Threshold (FST)*

Note: All testing procedures are to be ***attempted*** for participants in the Younger Age Cohort. If a child is unwilling to or unable to complete an examination, the procedure is to be skipped.

****If a site does not have the required equipment, participation in this test may be waived* ***with approval from the Coordinating Center.***

4.3.2 Vision Cohorts 1 & 2

1. Medical updates to include:
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - **Adults (18+ years at Baseline):** PROMIS®-29, MRDQ, ViSIO-PRO
   - **Adolescents (12-17 years at Baseline):** LVP-FVQ II, ViSIO-PRO
   - **Children (8-11 years at Baseline):** LVP-FVQ II, ViSIO-ObsRO
   - The PROs may be completed in person or remotely (phone or other remote methods) any time within six (6) months of the Baseline Visit (not required to be the same day as the rest of the Baseline Visit).
3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date and the ophthalmic examination was performed during the Registry/Screening Visit (i.e., not historical) – the ophthalmic examination testing procedure may be skipped.***
4. Visual Acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)
   - The visual acuity (VA) letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the VA testing procedure may be skipped.***
5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.

- ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the IOP testing procedure may be skipped.***

6. Color Vision
   - Desaturated (Lanthony D15)
7. Contrast Sensitivity
8. Spectral Domain Optical Coherence Tomography (SD-OCT)
   - Volume Scan
   - Vertical and Horizontal Scan
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the SD-OCT testing procedure may be skipped.***
9. Axial Length and Corneal Curvature Measurements
10. Optos Color Photos*
11. Optos Fundus Autofluorescence (FAF)*
12. Full-field Electroretinogram (ffERG)*
13. Full-field Stimulus Threshold (FST)*
14. Static Perimetry (SP)
    - Two (2) tests will be performed. The clinical site will compare the certified technician determined mean sensitivity from test one (1) versus test two (2).
      (a) If the absolute value of the difference between the two tests is ≤ 2.4 dB, then the participant passes static perimetry reliability criteria. A third test is not needed.
      (b) If the absolute value of the difference between the two tests is > 2.4 dB, then the participant does not pass static perimetry reliability criteria. A third test will be required.
    - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the SP performed during the Registry/Screening Visit may be considered the first test and does not need to be repeated. Only the second test will need to be performed at the Baseline Visit; the need for a third test will be assessed using Test 1 from the Registry/Screening Visit and Test 2 from the Baseline Visit.***
15. Fundus Guided Microperimetry (MP)*
    - Two (2) tests will be performed. The clinical site will compare the certified technician determined mean sensitivity from test one (1) versus test two (2).
      (a) If the absolute value of the difference between the two tests divided by the average between them is ≤ 50% OR the absolute value of the difference between the two tests is ≤ 0.5 dB, then the participant passes the microperimetry reliability criteria. A third test is not needed.

(b) If the absolute value of the difference between the two tests divided by the average between them is > 50% AND the absolute value of the difference between the two tests is > 0.5 dB, then the participant does not pass microperimetry reliability criteria. A third test will be required.

****If a site does not have the required equipment, participation in this test may be waived* ***with approval from the Coordinating Center.***

4.3.3 Vision Cohort 3

1. Medical updates to include
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - **Adults (18+ years at Baseline):** PROMIS®-29, MRDQ, ViSIO-PRO, ULV-VFQ-50
   - **Adolescents (12-17 years at Baseline):** LVP-FVQ II, ViSIO-PRO
   - **Children (8-11 years at Baseline):** LVP-FVQ II, ViSIO-ObsRO
   - The PROs may be completed in person or remotely (phone or other remote methods) any time within six (6) months of the Baseline Visit (not required to be the same day as the rest of the Baseline Visit).
3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date and the ophthalmic examination was performed during the Registry/Screening Visit – the ophthalmic examination testing procedure may be skipped.***
4. Visual Acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)
   - The visual acuity (VA) letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the Uni-Rare Clinical Site Manual of Procedures.
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the VA testing procedure may be skipped.***
5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.
   - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the IOP testing procedure may be skipped.***

6. Spectral Domain Optical Coherence Tomography (SD-OCT)
    - Volume Scan
    - Vertical and Horizontal Scan
    - ***If the Baseline Visit date is within 3 months of the Registry/Screening Visit testing date – the SD-OCT testing procedure may be skipped***
7. Axial Length and Corneal Curvature Measurements
8. Optos Color Photos*
9. Optos Fundus Autofluorescence (FAF)*
10. Full-field Stimulus Threshold (FST)*

****If a site does not have the required equipment, participation in this test may be waived* ***with approval from the Coordinating Center.***

Chapter 5: Natural History Study Follow-up Visits

5.1 Follow-up Schedule

Follow-up Visits or phone calls will occur annually. Participants in the Younger Age Cohort (YAC) and Vision Cohorts 1 and 2 will have annual in-person follow-up visits for four years after the Baseline Visit. Participants in Vision Cohort 3 will receive annual follow-up phone calls for three years after the Baseline Visit and will only return to the site for the last study visit (48-Month Visit).

The Baseline Visit date is considered study day zero (0) from which follow-up windows are timed. The Follow-up Visit date will be the date the Follow-up Visit testing procedures started. All Follow-up Visit testing procedures will be completed on the same date, other than the PROs as noted in Section 5.3 Follow-up Procedures.

5.2 Target Timelines

Target dates and windows for each study Follow-up Visit for all cohorts are shown below. Dates and windows are timed from Baseline Visit date.

Schedule for Follow-up Visits or Phone Calls

VISIT SCHEDULE	VISIT TYPE	TARGET DATE*	TARGET WINDOW*	ALLOWABLE WINDOW*
12-Month	YAC + Vision Cohort 1 & 2: In-person Visit Vision Cohort 3: Phone Call	52 Weeks	± 4 Weeks	± 6 Weeks
24-Month	YAC + Vision Cohort 1 & 2: In-person Visit Vision Cohort 3: Phone Call	104 Weeks	± 4 Weeks	± 6 Weeks
36-Month	YAC + Vision Cohort 1 & 2: In-person Visit Vision Cohort 3: Phone Call	156 Weeks	± 4 Weeks	± 6 Weeks
48-Month	All Cohorts In-person Visit	208 Weeks	± 4 Weeks	± 6 Weeks

*Timed from Baseline Visit Date

The goal is for all participants to complete all scheduled study visits. However, participants who (because of unforeseen circumstances) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. Additional office visits may occur as needed.

5.3 Follow-up Visit Testing Procedures

The following procedures will be performed at the Follow-Up Visits, unless otherwise specified. An overview of the equipment and certification requirements for all testing is in section 6.1. All ocular testing will be performed in each eye, OD first and then OS. Follow-up Visit procedures will last approximately three (3) hours. The testing procedures are detailed in the **Uni-Rare Clinical Site Manual of Procedures**.

5.3.1 Younger Age Cohort

1. Medical updates to include:
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - ViSIO-ObsRO
   - The PROs may be completed in person or remotely (phone or other remote methods) any time within the Allowable Window of the associated visit (not required to be the same day as the rest of the Follow-up Visit).
3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
4. Visual Acuity (including refraction, HOTV, BRVT if needed, LLVA if needed)
   - The visual acuity (VA) Snellen score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.
5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.
6. Color Vision
   - Desaturated (Lanthony D15)
7. Spectral Domain Optical Coherence Tomography (SD-OCT)
   - Volume Scan
   - Vertical and Horizontal Scan
   - If unable to perform OCT testing on the Heidelberg Spectralis, a site may use the handheld Bioptogen/Envisu to perform OCT testing for qualitative purposes **with approval from the Coordinating Center**.
8. Axial Length and Corneal Curvature Measurements
9. Optos Fundus Autofluorescence (FAF)*

10. Full-field Electroretinogram (ffERG)*
    - Complete at 48-Month Follow-up Visit Only
11. Full-field Stimulus Threshold (FST)*

5.3.1.1 Age-Up Procedures

Participants in the Younger Age Cohort who turn 8 years old (age-up) during the NHS study period should attempt to have static perimetry, microperimetry, and contrast sensitivity testing performed at the next study visit after they turn 8 years old and at every subsequent visit, until the end of the study period.

12. Static Perimetry (SP)
13. Fundus Guided Microperimetry (MP)*
14. Contrast Sensitivity

Note: All testing procedures are to be ***attempted*** for participants in the Younger Age Cohort. If a child is unwilling to or unable to complete an examination, the procedure is to be skipped.

****If a site does not have the required equipment, participation in this test may be waived* ***with approval from the Coordinating Center.***

5.3.2 Vision Cohorts 1 & 2

1. Medical updates to include:
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - Complete at 24-Month and 48-Month Follow-up Visits Only
   - **Adults (18+ years at Baseline):** PROMIS®-29, MRDQ, ViSIO-PRO
   - **Adolescents (12-17 years at Baseline):** LVP-FVQ II, ViSIO-PRO
   - **Children (8-11 years at Baseline):** LVP-FVQ II, ViSIO-ObsRO
   - The PROs may be completed in person or remotely (phone or other remote methods) any time within the Allowable Window of the associated visit (not required to be the same day as the rest of the Follow-up Visit).
3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
4. Visual Acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)

- The visual acuity (VA) letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.

5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.
6. Color Vision
   - Desaturated (Lanthony D15)
7. Contrast Sensitivity
8. Spectral Domain Optical Coherence Tomography (SD-OCT)
   - Volume Scan
   - Vertical and Horizontal Scan
9. Axial Length and Corneal Curvature Measurements
   - Only individuals who are under 18 years old at the Baseline Visit will continue to have measurements taken at every annual visit until study completion.
10. Optos Fundus Autofluorescence (FAF)*
11. Full-field Electroretinogram (ffERG)*
    - Complete at 48-Month Follow-up Visit Only
12. Full-field Stimulus Threshold (FST)*
13. Static Perimetry (SP)
14. Fundus Guided Microperimetry (MP)*

If a site does not have the required equipment, participation in this test may be waived **with approval from the Coordinating Center.*

5.3.3 Vision Cohort 3

Phone contact will be scheduled at 12-, 24-, and 36-Month intervals. The purpose of the phone contact will be to keep the participants engaged in the study during the interim between the Baseline and 48-Month Follow-up Visits and to keep contact information updated. Changes in medications and AEs will also be collected.

The following will only be performed at <u>48-Month Visit</u>:

1. Medical updates to include
   - New or changed adverse events (AEs)
   - New ocular procedures
   - New or changed medications
2. Patient Reported Outcomes (PROs)
   - **Adults (18+ years at Baseline):** PROMIS®-29, MRDQ, ViSIO-PRO, ULV-VFQ-50

- **Adolescents (12-17 years at Baseline):** LVP-FVQ II, ViSIO-PRO
- **Children (8-11 years at Baseline):** LVP-FVQ II, ViSIO-ObsRO
- The PROs may be completed in person or remotely (phone or other remote methods) any time within the Allowable Window of the associated visit (not required to be the same day as the rest of the Follow-up Visit).

3. Complete ophthalmic examination to include:
   - Slit lamp biomicroscopy
   - Indirect ophthalmoscopy
4. Visual Acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)
   - The visual acuity (VA) letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the **Uni-Rare Clinical Site Manual of Procedures**.
5. Intraocular Pressure (IOP)
   - IOP measurements are to be taken prior to pupil dilation.
6. Spectral Domain Optical Coherence Tomography (SD-OCT)
   - Volume Scan
   - Vertical and Horizontal Scan
7. Axial Length and Corneal Curvature Measurements
   - Only individuals who were under 18 years old at the Baseline Visit will have measurements taken at 48M visit.
8. Optos Fundus Autofluorescence (FAF)*
9. Full-field Stimulus Threshold (FST)*

****If a site does not have the required equipment, participation in this test may be waived* ***with approval from the Coordinating Center.***

5.3.4 Unscheduled Visits

Testing procedures at unscheduled visits are at the Investigator's discretion. However, it is recommended that procedures performed during these visits follow the standard protocol for each procedure and be performed by certified personnel. Unscheduled visits will be recorded on the FFB Consortium study website. Study images taken during unscheduled visits do not require submission to the study website.

Chapter 6: Testing Procedures and Questionnaires

6.1 Study Procedure Requirements

The study procedure instructions are detailed in the **Uni-Rare Clinical Site Manual of Procedures**. An overview of the equipment and certification requirements for all testing are provided in the table below.

Study Procedures	Description	Equipment Required (If applicable)	Site Personnel Delegation
Investigator taking overall responsibility for a visit	Oversees that consent process was performed in accordance with IRB/EC requirements; signs off on all eCRFs for a participant, eCRF edits, and protocol deviations.	N/A	Certified investigator
Coordinator taking responsibility for the visit	Oversees the data entry aspect of the visit; addresses protocol queries and signs off on deviations.	N/A	Certified coordinator
Informed Consent Form (ICF) Process	Explanation/review of study with the potential participant, including signature on the ICF.	N/A	Certified investigator or coordinator as permitted by the IRB/EC
Signature of Informed Consent Form	The participant and/or LAR sign the ICF. The person obtaining the ICF will also sign.	N/A	Certified investigator or coordinator as permitted by the IRB/EC
Data entry on study website	Data collected from the study participant will be directly entered on the FFB Study Website (strongly encouraged) or written on the paper CRF and transcribed on the FFB Study Website within seven (7) days.	Computer and internet connection	Certified coordinator or certified investigator with additional study website certification
Collect information regarding medical history, demographics, adverse events, medications	Sites will collect medical history, demographic information, Aes, and medications from the participant during each visit. This information can be confirmed by requesting medical records if needed.	N/A	Certified investigator or coordinator
Patient Reported Outcome (PRO)	There are six (6) questionnaires depending on age and Vision Cohort (details in section 6.2).	Study will provide	Certified investigator or coordinator
Ocular Exam	Including slit lamp biomicroscopy and indirect ophthalmoscopy	Any equipment is acceptable	Certified investigator
Intraocular Pressure (IOP)	Measurement of the fluid pressure inside the eye	Any equipment is acceptable	Clinical site personnel performing this test does not require a study specific certification. However, they must be trained and delegated by the PI per the SSDL.

Study Procedures	Description	Equipment Required (If applicable)	Site Personnel Delegation
Visual Acuity – Refraction	Refraction is done as a routine part of an eye exam to achieve best corrected visual acuity measures.	N/A	Clinical site personnel certified for refraction
Visual Acuity – ETDRS	Traditional measure of central visual function that represents foveal cone function.	EVA system or ETDRS charts	Clinical site personnel certified for VA (including ETDRS)
Visual Acuity – LLVA	Measures vision function in low luminance conditions	EVA system or ETDRS charts 2.0 neutral density filter to be provided by study	Clinical site personnel certified for VA (including LLVA)
Visual Acuity – BRVT	A three-level hierarchy for visual acuity testing better suited for low vision participants	BRVT charts provided by study	Clinical site personnel certified for BRVT
Visual Acuity – HOTV	Pediatric measure of central visual function that represents foveal cone function.	HOTV chart and lap card provided by study	Clinical site personnel certified for VA (including HOTV)
Color Vision	Measures the type and severity of color blindness	Lanthony D15 provided by study	Clinical site personnel performing this test does not require a study specific certification. However, they must be trained and delegated by the PI per the SSDL.
Contrast Sensitivity	Measure ability to distinguish between increments of light versus dark	CSV-1000E provided by study	Clinical site personnel performing this test does not require a study specific certification. However, they must be trained and delegated by the PI per the SSDL.
Spectral Domain Optical Coherence Tomography (SD-OCT) – Volume Scan	Scans provide objective, non-invasive measures of retinal structure	Heidelberg Spectralis**	Clinical site personnel certified for SD-OCT
Spectral Domain Optical Coherence Tomography (SD-OCT) – Vertical and Horizontal Scan	Scans provide objective, non-invasive measures of retinal structure	Heidelberg Spectralis**	Clinical site personnel certified for SD-OCT and vertical and horizontal scan
Axial Length and Corneal Curvature	Axial length measures the distance between the anterior and posterior poles of the eye. Corneal curvature determines the power of the cornea.	Any equipment is acceptable	Clinical site personnel performing this test does not require a study specific certification. However, they must be trained and delegated by the PI per the SSDL.

Study Procedures	Description	Equipment Required (If applicable)	Site Personnel Delegation
Optos Color Photos	Images provide objective, non-invasive visualization of the photoreceptor layer and RPE	Optos*	Clinical site personnel certified for Optos Color photos
Optos Fundus Autofluorescence (FAF)	Images provide objective, non-invasive map of lipofuscin in RPE	Optos*	Clinical site personnel certified for Optos FAF
Full-field Electroretinogram (ffERG)	Measures rod- and cone-mediated parts of the visual field	Diagnosys Espion*	Clinical site personnel certified for ffERG
Full-field Stimulus Threshold (FST)	Measures rod- and cone-mediated parts of the visual field	Diagnosys Espion*	Clinical site personnel performing this test does not require a study specific certification. However, they must be trained and delegated by the PI per the SSDL.
Static Perimetry (SP)	Measures sensitivity thresholds at specified test locations	Octopus 900 Pro (GATE Protocol)	Clinical site personnel certified for SP
Fundus guided microperimetry (MP)	Measures sensitivity thresholds at specified test locations	MAIA*	Clinical site personnel certified for MP
Kinetic Perimetry (KP)	Measures sensitivity thresholds at specified test locations	Any equipment is acceptable	(Historical) Does not need to be performed by study certified personnel or recorded in the SSDL

*If site does not have required equipment, participation in this test may be waived **with approval from the Coordinating Center**

If Younger Age Cohort participant is unable to perform OCT testing on the Heidelberg Spectralis, a site may use the handheld Bioptogen/Envisu to perform OCT testing for qualitative purposes **with approval from the Coordinating Center.

6.2 Questionnaires

The following questionnaires will be administered in the study by a certified investigator or coordinator. Each questionnaire takes about 15 minutes to administer.

Questionnaire	Type	Description	Vision Cohort	Age at Baseline
Michigan Retinal Degeneration Questionnaire (MRDQ)	Vision Function	The MRDQ is a psychometrically validated patient-reported outcome measure for inherited retinal degenerations questionnaire which consists of fifty-nine (59) questions measuring seven (7) unidimensional domains: central vision, color vision, contrast sensitivity, scotopic function, photopic peripheral vision, mesopic peripheral vision, and photosensitivity.	All	Adults ≥18 years

PROMIS-29® (Patient-Reported Outcomes Measurement Information System®)	Global Physical, Mental, and Social Health	The PROMIS®-29 contains items from seven PROMIS domains: depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities. The seven domains cover the most relevant areas of self-reported health for most people with chronic illness. There is also one 11-point rating scale for pain intensity.	All	Adults ≥18 years
Visual Symptom and Impact Outcomes Patient Reported Outcome (ViSIO-PRO)	Vision Function and HRQoL	The ViSIO-PRO instrument is designed to assess visual function symptoms, impacts on functional vision, and impacts on wider health-related quality of life (HRQoL). It has been designed for completion by adolescents (12-17) and adults (18 +) with retinitis pigmentosa (RP).	All	Adolescents (12-17 years) & Adults (≥18 years)
Visual Symptom and Impact Outcomes Observer Reported Outcome (ViSIO-ObsRO)	Vision Function and HRQoL	The ViSIO-ObsRO instrument is designed to assess visual function symptoms, impacts on functional vision, and impacts on wider health-related quality of life (HRQoL). It has been designed for completion by parents/caregivers of children with retinitis pigmentosa (RP) aged 3-11 years.	All	Children 4-11 years
L. V. Prasad-Functional Vision Questionnaire (LVP-FVQ II)	Vision Function	The LVP-FVQ-II questionnaire consists of 23 questions. The questionnaire is used to assess self-reported difficulties in performing daily tasks in children with visual impairment.	All	Adolescents (12-17 years) & Children (8-11 years)
Ultra-Low Vision Visual Functioning Questionnaire (ULV-VFQ-50)	Vision Function	The ULV-VFQ-50 psychometrically evaluates a visual functioning questionnaire (VFQ) in an ultra-low vision (ULV) population	Vision Cohort 3	Adults ≥18 years

Chapter 7: Unanticipated Problem and Adverse Event Reporting

7.1 Unanticipated Problems

Site investigators will promptly report all unanticipated problems meeting the criteria below on an electronic case report form (eCRF). Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm).

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a laboratory.

These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting to fulfill the reporting obligations of the HRPP.

7.2 Adverse Events

The following section on adverse events applies to the Natural History Study phase of the study.

7.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures whether the event is considered related.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event: (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).

- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition.

Note: As this is a Natural History Study, the Investigator(s) will make the categorical determinations of Adverse Events, as described above, and will report each determination to the Coordinating Center, as per data collection.

7.2.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes all events meeting the definition of an adverse event.

All reportable Adverse Events whether volunteered by the participant, discovered by study personnel during questioning, or detected through ophthalmological examination, laboratory test, or other means will be reported on an adverse event form online.

The purpose of AE collection for the Uni-Rare study will be to provide historical controls for future clinical trials. As a no greater than minimal risk study, AEs do not require any specific reporting to regulatory or oversight bodies. However, each Principal Investigator (PI) is responsible for abiding by any other reporting requirements specific to their IRB or equivalent ethics oversight committee.

7.2.3 Relationship of Adverse Event to Study Procedure

The study Investigator(s) will assess the relationship of any adverse event to be related or unrelated to a study procedure by determining if there is a reasonable possibility that the adverse event may have been caused by the study procedure.

To ensure consistency of adverse event causality assessments, the Investigator(s) should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study procedure, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study procedure; and/or the adverse event abates or resolves upon discontinuation of the study procedure.

No

Evidence exists that the adverse event has an etiology other than the study procedure (for example, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study procedure.

7.2.4 Severity (Intensity) of Adverse Event

A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

The severity (intensity) of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe.

1. **MILD:** Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
2. **MODERATE:** Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
3. **SEVERE:** Interrupts a participant's usual daily activities and causes severe discomfort.

7.2.5 Expectedness

As this is a Natural History Study, the expectedness for a serious adverse event will not be assessed.

7.2.6 Coding of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). To facilitate coding, the site will enter a preliminary MedDRA code

7.2.7 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the Investigator(s) as follows:

1. **RECOVERED/RESOLVED (COMPLETE RECOVERY)** – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
2. **RECOVERED/RESOLVED WITH SEQUELAE** – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE/SAE stop date.
3. **FATAL** – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
4. **ONGOING NOT RECOVERED/NOT RESOLVED** – An ongoing AE/SAE is defined as an ongoing event with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

5. **ONGOING (MEDICALLY STABLE)** – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a participant completes the study (or withdraws), they will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study.

Note: Participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

7.3 Timing of Event Reporting

Investigator(s) are responsible for reporting Adverse Events on the electronic case report form (eCRF) through the study website in a timely manner.

Each Principal Investigator (PI) is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board (IRB) or Ethics Committee (EC). Where the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events regardless of whether they are expected/anticipated and regardless of whether they are fatal or life-threatening within seven (7) calendar days.

Chapter 8: Miscellaneous Considerations

8.1 New or Ongoing Medical Conditions and Medications

8.1.1 Pre-Existing Conditions

Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the study (for example, prior myocardial infarction or stroke).

8.1.2 Medications

All medication for the treatment of chronic pre-existing conditions, medical conditions, and/or adverse events that the participant is currently taking at screening and during the study should be recorded. Certain nutraceuticals and preventative treatments that are of interest to the study should also should be recorded.

8.1.3 Medical Conditions During the Natural History Study

In addition to conditions meeting the reporting requirements for an adverse event or as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (for example, not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment. These will be reported as adverse events. See chapter 7 for more detail.

8.2 Prohibited Medications, Treatments, and Procedures During the Natural History Study

8.2.1 Prohibited Medications and Treatment for Retinal Degeneration

Participants who are ***enrolled into the NHS*** should not administer IRD treatments during the study. This includes enrolling into an experimental treatment trial of underlying conditions related to the causal gene during the 4-year study duration. However, if the participants enroll in a treatment trial the Executive Committee will be consulted and will determine if the participant will continue in the study.

Examples of prohibited medications and treatments include, but are not limited to the following:

- use of ocular stem cell or gene therapy
- ocriplasmin
- ophthalmic oligonucleotide
- Ozurdex (dexamethasone)
- Iluvien
- Yutiq (fluocinolone acetonide) intravitreal implant

8.2.2 Intraocular Surgical Procedures

Participants ***enrolled into the NHS***, who have intraocular surgery during the study, will have follow-up visits timed either before the surgery date or at least three (3) months after the surgery date, to minimize the impact on the natural history outcome measures. Clinical sites will make reasonable efforts to schedule the participant's follow-up visit as close to the visit target window as possible.

8.2.3 Treatment for Cystoid Macular Edema (CME)

Participants ***enrolled into the NHS***, who need to receive treatment for CME during the study, may do so without affecting their participation in the study.

8.3 Pregnancy Reporting

If a pregnancy occurs, the participant will remain in the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven (7) days of the site's discovery of the pregnancy (including at screening) and the Confirmed Pregnancy Notification Worksheet will be completed within seven (7) calendar days. Sites will collect concomitant medications throughout the pregnancy. If an Adverse Event occurs because of the pregnancy, then the site will record the Adverse Event on the Adverse Event form.

8.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

8.5 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

8.6 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information (PHI) gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

Chapter 9: Statistical Considerations

The approach to sample size (N) and statistical analyses are summarized below.

9.1 Sample Size Approach

The following is a framework for evaluating and justifying within-gene sample size for any gene in the Uni-Rare Study.

9.1.1 General Considerations

Both eyes of a participant will be assessed for the main ocular measures of interest. Thus, if there are N participants, 2N eyes will be available for analysis. However, outcome measures from two (2) eyes of a person are typically strongly correlated ($r \geq 0.5$). The contribution of information from the two (2) eyes in this case is $(2/(1+r))$ instead of two (2). Values for the multiplier to the number of participants to obtain an effective sample size are given below in **Table 9-1**. The correlation between eyes (inter-eye correlation) for each outcome measure is not known. We assume an inter-eye correlation of 0.8 throughout all sample size calculations throughout section 1.1. This assumption is conservative in that it requires a higher number of participants than lower plausible values of r.

Table 9-1. Multiplier to Obtain Effective N Based on Inter-Eye Correlation

r	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Multiplier for Effective N	2.00	1.82	1.67	1.54	1.43	1.33	1.25	1.18	1.11	1.05	1.00

9.1.2 Registry Sample Size Considerations

As noted in section 2.1, the Registry recruitment will remain open until a total of 1,500 participants meeting *Registry Cohort Criteria* are enrolled, with **a maximum of 100 participants enrolled within any gene.** The following Registry sample size considerations focus on **Registry Objective 2** (see section 1.3).

Registry Objective 2 (Cross-Sectional Phenotype Characterization)

- **Registry Objective 2** is to characterize cross-sectional retinal dystrophy associated with disease-causing genetic variants using functional and structural measures, **within gene**.
- For a given gene, the potential sample size for the gene will impact the precision around the point estimates for the key measures of interest.
- **Table 9-2, 9-3, and 9-4** provide the half-width of the 95% confidence interval (CI) around the estimated cross-sectional mean value, for three key measures of interest (visual acuity, OCT EZ area, and SP V_{tot}, respectively) under different possible sample sizes and standard deviations (SD) of the distribution of the cross-sectional measure. The larger the SD and/or the smaller the sample size, the wider the CI, meaning the range of possible true values grows.

Table 9-2. Half-Width of 95% Confidence Intervals Around the Estimated Mean Cross-Sectional Visual Acuity

	Sample Size *(effective sample size after adjusting for inter-eye correlation r=0.8)*									
	N=10	**N=20**	**N=30**	**N=40**	**N=50**	**N=60**	**N=70**	**N=80**	**N=90**	**N=100**
	(11)	***(22)***	***(33)***	***(44)***	***(56)***	***(67)***	***(78)***	***(89)***	***(100)***	***(111)***
SD=5	3.4	2.2	1.8	1.5	1.3	1.2	1.1	1.1	1.0	0.9
SD=10	6.7	4.4	3.5	3.0	2.7	2.4	2.3	2.1	2.0	1.9
SD=15	10.1	6.7	5.3	4.6	4.0	3.7	3.4	3.2	3.0	2.8
SD=20	13.4	8.9	7.1	6.1	5.4	4.9	4.5	4.2	4.0	3.8

Units = letter score

Table 9-3. Half-Width of 95% Confidence Intervals Around the Estimated Mean Cross-Sectional OCT Ellipsoid Zone Area

	Sample Size *(effective sample size after adjusting for inter-eye correlation r=0.8)*									
	N=10	**N=20**	**N=30**	**N=40**	**N=50**	**N=60**	**N=70**	**N=80**	**N=90**	**N=100**
	(11)	***(22)***	***(33)***	***(44)***	***(56)***	***(67)***	***(78)***	***(89)***	***(100)***	***(111)***
SD=2	1.3	0.9	0.7	0.6	0.5	0.5	0.5	0.4	0.4	0.4
SD=5	3.4	2.2	1.8	1.5	1.3	1.2	1.1	1.1	1.0	0.9
SD=8	5.4	3.5	2.8	2.4	2.1	2.0	1.8	1.7	1.6	1.5
SD=10	6.7	4.4	3.5	3.0	2.7	2.4	2.3	2.1	2.0	1.9

Units = mm^2

Table 9-4. Half-Width of 95% Confidence Intervals Around the Estimated Mean Cross-Sectional Static Perimetry V_{tot} (Hill of Vision)

	Sample Size *(effective sample size after adjusting for inter-eye correlation r=0.8)*									
	N=10	**N=20**	**N=30**	**N=40**	**N=50**	**N=60**	**N=70**	**N=80**	**N=90**	**N=100**
	(11)	***(22)***	***(33)***	***(44)***	***(56)***	***(67)***	***(78)***	***(89)***	***(100)***	***(111)***
SD=10	6.7	4.4	3.5	3.0	2.7	2.4	2.3	2.1	2.0	1.9
SD=15	10.1	6.7	5.3	4.6	4.0	3.7	3.4	3.2	3.0	2.8
SD=20	13.4	8.9	7.1	6.1	5.4	4.9	4.5	4.2	4.0	3.8
SD=25	16.8	11.1	8.9	7.6	6.7	6.1	5.6	5.3	5.0	4.7

Units = dB-sr

Registry Sample Size Example

The following is an example of using the tables above and a set of assumptions for a given gene of interest to determine the precision of cross-sectional estimates of key measures.

Gene	**BBS1**	
Anticipated Sample Size	**50**	
Key Measure	**Assumed Standard Deviation (SD)**	**Precision around estimated mean value (half-width of 95% CI)**
Visual Acuity	**10**	2.7
OCT EZ Area	**5**	1.3
SP V_{tot}	**20**	5.4

Assumptions based on Mean (standard deviation) of RUSH2A baseline V_{tot}, VA, and OCT EZ RUSH2A shown below

	Overall	**USH2**	**ARRP**
VA	**77.9 (11.7)**	**76.5 (12.4)**	**80.3 (10.2)**
OCT EZ area	**3.6 (5.6)**	**3.1 (5.7)**	**4.3 (5.6)**
SP V_{tot}	**27.8 (23.7)**	**22.5 (21.5)**	**37.1 (24.7)**

9.1.3 Natural History Study Sample Size Considerations

As noted in section 4.1, the designation of **NHS Target Genes** will be made by the Executive Committee on an ongoing basis and may depend on funding resources as well as Registry enrollment numbers within gene. The Natural History Study sample size for each gene will depend on the Registry enrollment. Since the within-gene Registry limit is 100 participants, this will be the maximum sample size for **NHS Target Genes**.

The following NHS sample size considerations focus on **NHS Objectives 1-3** (see section 1.3). For all of these objectives, the following principles will apply in the sections below:

- For simplicity across all measures, **percent change** will be considered for sample size justification purposes.
- Also for simplicity, although statistical analyses will include the data from each annual visit, **change from baseline to four (4) years** will be considered for sample size justification purposes.
- This simplistic approach will produce conservative estimates, in terms of precision. Future work will include exploring impact of sample sizes on these estimates when using all available longitudinal data, for example, how much will this improve precision. This will be documented separately.

NHS Objective 1 (Natural History)

- **NHS Objective 1** is to characterize the natural history of retinal degeneration associated with disease-causing genetic variants over 4 years, using functional, structural, and patient-reported outcome measure, **within gene.**
- For a given gene, the potential sample size for the gene will impact the precision around the point estimates for changes in the outcome measures of interest.
- **Table 9-5** provides the half-width of the 95% confidence interval (CI) around the estimated percent change in outcome measures under different possible sample sizes and standard deviations (SD) of the distribution of the percent change for any given outcome measure. The larger the SD and/or the smaller the sample size, the wider the CI, meaning the range of possible true values grows.

Table 9-5. Half-Width of 95% Confidence Intervals Around the Estimated Percent Change

	Sample Size *(effective sample size after adjusting for inter-eye correlation r=0.8)*									
	N=10	**N=20**	**N=30**	**N=40**	**N=50**	**N=60**	**N=70**	**N=80**	**N=90**	**N=100**
	(11)	***(22)***	***(33)***	***(44)***	***(56)***	***(67)***	***(78)***	***(89)***	***(100)***	***(111)***
SD=5%	3%	2%	2%	2%	1%	1%	1%	1%	1%	1%
SD=10%	7%	4%	4%	3%	3%	2%	2%	2%	2%	2%
SD=20%	13%	9%	7%	6%	5%	5%	5%	4%	4%	4%
SD=30%	20%	13%	11%	9%	8%	7%	7%	6%	6%	6%
SD=40%	27%	18%	14%	12%	11%	10%	9%	8%	8%	8%
SD=50%	34%	22%	18%	15%	13%	12%	11%	11%	10%	9%
SD=60%	40%	27%	21%	18%	16%	15%	14%	13%	12%	11%

NHS Objective 2 (Structure-Function Relationship)

- **NHS Objective 2** is to explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with disease-causing genetic variants, **within gene.**
- For a given gene, the potential sample size for the gene will impact the precision around the point estimates for the correlation between the outcome measures of interest.
- **Table 9-6** provides the 95% confidence intervals around the estimated correlation between outcome measures under different possible sample sizes and Pearson correlation coefficients.
    - The Pearson correlation coefficient (r) can be used to assess the correlation between two different outcome measures. The distribution of r is not symmetric; therefore, CIs for the estimated correlation coefficient are not symmetric. A transformation of r ($z = 0.5 * \ln((1+r)/1-r)$) is used to create a variable that is asymptotically distributed N (0, 1/(sqrt(N-3))) under the null hypothesis that r=0.

Table 9-6. 95% Confidence Intervals for an Observed Value of the Correlation between Outcome Measures.

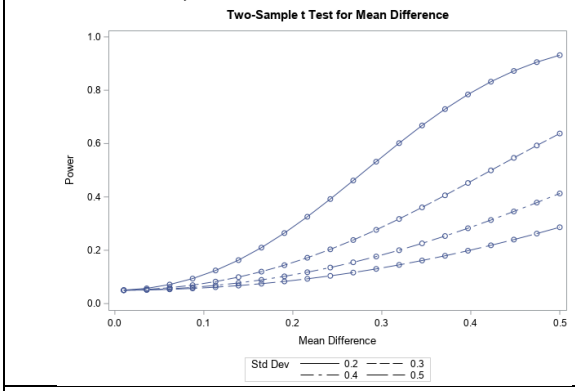
	Sample Size *(effective sample size after adjusting for inter-eye correlation r=0.8)*									
	N=10	**N=20**	**N=30**	**N=40**	**N=50**	**N=60**	**N=70**	**N=80**	**N=90**	**N=100**
	(11)	***(22)***	***(33)***	***(44)***	***(56)***	***(67)***	***(78)***	***(89)***	***(100)***	***(111)***
r=0.3	(-0.41,0.78)	(-0.16,0.66)	(-0.07,0.60)	(-0.01,0.56)	(0.02,0.53)	(0.05,0.51)	(0.07,0.50)	(0.09,0.49)	(0.10,0.48)	(0.11,0.47)
r=0.4	(-0.31,0.82)	(-0.05,0.72)	(0.05,0.66)	(0.10,0.63)	(0.14,0.61)	(0.16,0.59)	(0.18,0.58)	(0.20,0.57)	(0.21,0.56)	(0.22,0.55)
r=0.5	(-0.19,0.86)	(0.07,0.77)	(0.17,0.73)	(0.22,0.70)	(0.26,0.68)	(0.28,0.67)	(0.30,0.66)	(0.31,0.65)	(0.33,0.64)	(0.34,0.63)
r=0.6	(-0.05,0.89)	(0.21,0.82)	(0.31,0.79)	(0.35,0.77)	(0.39,0.75)	(0.41,0.74)	(0.42,0.73)	(0.44,0.72)	(0.45,0.72)	(0.46,0.71)
r=0.7	(0.13,0.92)	(0.37,0.87)	(0.45,0.85)	(0.50,0.83)	(0.52,0.82)	(0.54,0.81)	(0.56,0.80)	(0.57,0.80)	(0.58,0.79)	(0.58,0.79)
r=0.8	(0.34,0.95)	(0.55,0.92)	(0.62,0.90)	(0.65,0.89)	(0.67,0.88)	(0.69,0.88)	(0.70,0.87)	(0.70,0.87)	(0.71,0.86)	(0.72,0.86)
r=0.9	(0.62,0.98)	(0.76,0.96)	(0.80,0.95)	(0.82,0.95)	(0.83,0.94)	(0.84,0.94)	(0.84,0.94)	(0.85,0.93)	(0.85,0.93)	(0.85,0.93)

NHS Objective 3 (Risk Factors for Progression)

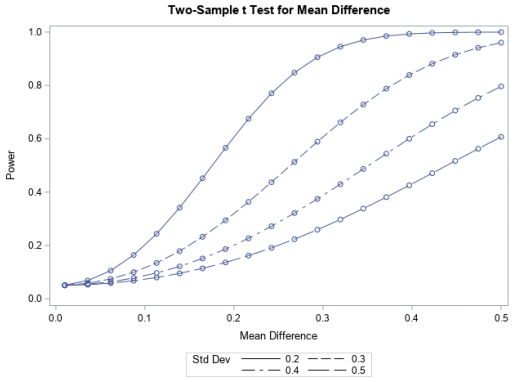
- **NHS Objective 3** is to explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with disease-causing genetic variants, **within gene.**
- For a given gene, the potential sample size for the gene will impact the power to detect differences in changes from baseline among subgroups of interest.
- **Figure 9-1** evaluates the **power to detect differences** in percent change from baseline to four (4) years among two (2) subgroups of equally distributed sizes, under various assumptions of true mean difference (x-axis) and standard deviation (SD) of the distribution of percent change. If subgroups are not equally sized, the smallest detectable difference (with the same power) will be larger. All calculations are based on a Type I (α) error rate of 0.05.
    - For example, with a total sample size of twenty (20), assuming ten (10) in each of two (2) subgroups, to have power of 80% or more, the true difference needs to be approximately 1.25 SDs (a mean difference of 25% if the SD of the percent change over four (4) years 20%)
- **Also Note:** *Within-subgroup* point estimates and CIs will also be important. **Table 9-3** above can be applied to potential subgroup sample sizes as well to consider the precision that would be observed.

Figure 9-1 Power to Detect Differences in Subgroups

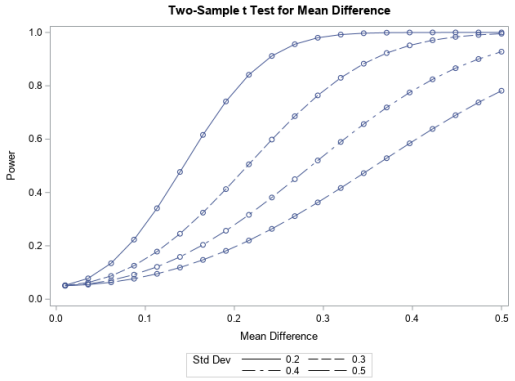
Total Sample Size N= 10
(N=11 effective sample size after adjusting for inter-eye correlation r=0.8)



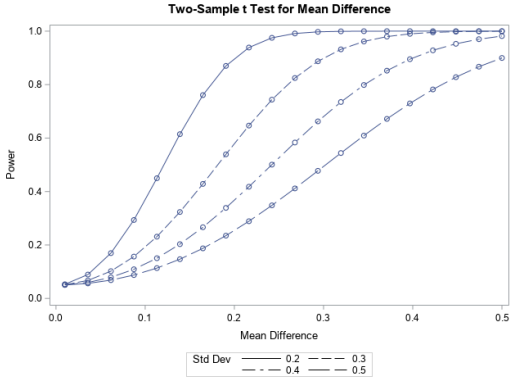
Total Sample Size N= 20
(N=22 effective sample size after adjusting for inter-eye correlation r=0.8)



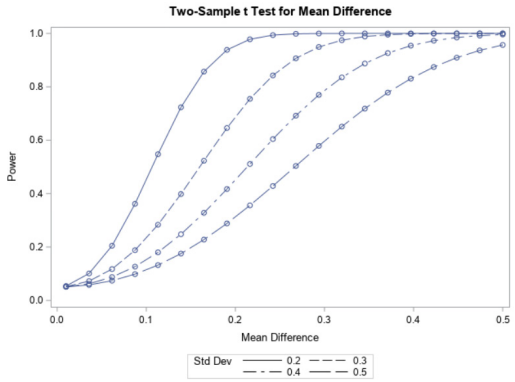
Total Sample Size N= 30
(N=33 effective sample size after adjusting for inter-eye correlation r=0.8)



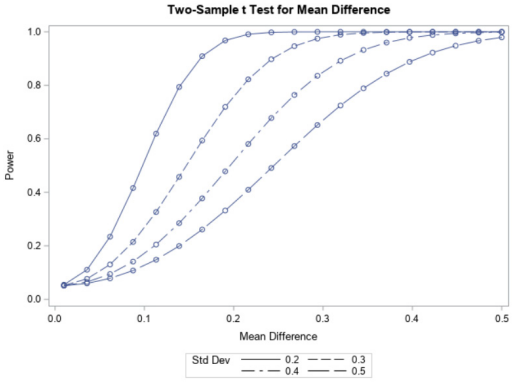
Total Sample Size N= 40
(N=44 effective sample size after adjusting for inter-eye correlation r=0.8)



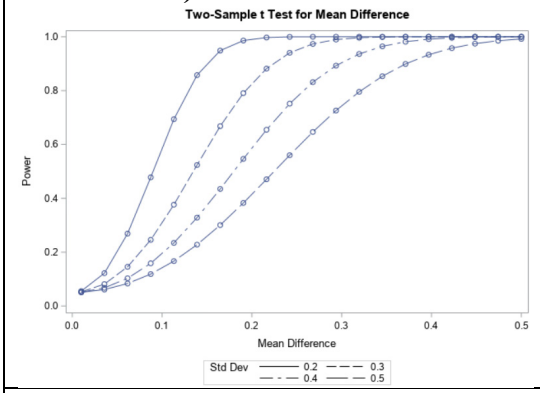
Total Sample Size N= 50
(N=56 effective sample size after adjusting for inter-eye correlation r=0.8)



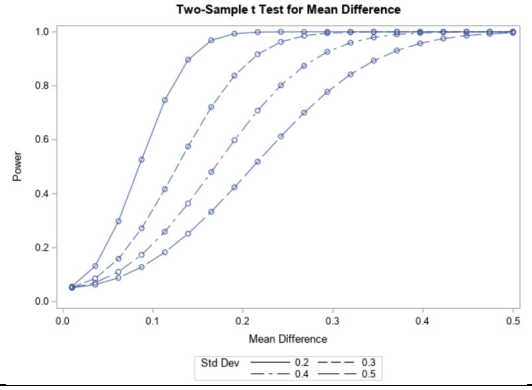
Total Sample Size N= 60
(N=67 effective sample size after adjusting for inter-eye correlation r=0.8)



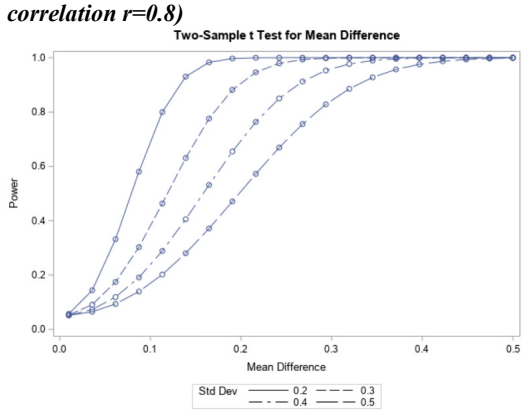
Total Sample Size N= 70
(N=78 effective sample size after adjusting for inter-eye correlation r=0.8)



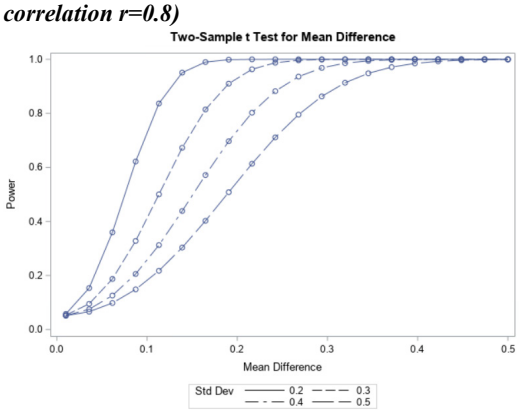
Total Sample Size N= 80
(N=89 effective sample size after adjusting for inter-eye correlation r=0.8)



Total Sample Size N= 90
(N=100 effective sample size after adjusting for inter-eye correlation r=0.8)



Total Sample Size N= 100
(N=111 effective sample size after adjusting for inter-eye correlation r=0.8)



NHS Sample Size Example

The following is an example template of using the tables above and a set of assumptions for a given gene of interest to determine the impact on NHS Objectives.

Target Gene	**MYO7A**
Target Sample Size	**50**
Data to consider for assumptions	**Data** • **RUSH2A Data – Mean (SD) percent change at 24M** o Visual Acuity: -2.3 (5.1)% o OCT EZ area: -2.2 (21.8)% o Static Perimetry HOV: -12.4 (28.2)% **Assume:** • Inter-eye correlation = 0.8 • SD for percent change at 4 years o Visual Acuity → 5% o OCT EZ area → 20% o Static Perimetry HOV → 30%

<table>
<tr><td>NHS Objective 1 (Natural History)</td><td>The half-width of a 95% CI around the point estimate for mean percent change at 4 years would be
<table>
<tr><th>Visual Acuity</th><th>OCT EZ area</th><th>Static Perimetry HOV</th></tr>
<tr><td>1%</td><td>5%</td><td>8%</td></tr>
</table></td></tr>
<tr><td>NHS Objective 2 (Structure-Function Relationship)</td><td>The 95% CI around correlation between any two outcome measures would be
<table>
<tr><td>if the observed correlation r = 0.3</td><td>(0.02, 0.53)</td></tr>
<tr><td>if the observed correlation r = 0.5</td><td>(0.26, 0.68)</td></tr>
<tr><td>if the observed correlation r = 0.8</td><td>(0.67, 0.88)</td></tr>
</table></td></tr>
<tr><td>NHS Objective 3 (Risk Factors for Progression)</td><td>A comparison of two equal-sized subgroups (N=25 each group) would have about 80% power to conclude there is a difference if the true difference is
<table>
<tr><th>Visual Acuity</th><th>OCT EZ area</th><th>Static Perimetry HOV</th></tr>
<tr><td>4%</td><td>15%</td><td>23%*</td></tr>
</table>
[Type I (α) error rate of 0.05]
* For example, if one subgroup had a percent change of 13%, the other subgroup would need a percent change of 36% to statistically conclude there is a difference.</td></tr>
</table>

9.2 Data Analysis

The analysis plans below are written with respect to the majority of outcomes of interest.

Analyses will include data on both eyes for each participant, and confidence intervals will adjust for correlation between two (2) eyes of the same participant.

9.2.1 Registry Data Analysis

The following Registry data analysis considerations focus on **Registry Objective 2** (see section 1.3). ***Applicability of <u>within-gene</u> objectives will depend on <u>within-gene</u> sample size as noted below. <u>If less than 20,</u> limit primary objective to describing the cohort in the form of case histories. Objectives may still be explored depending on the needs for a specific gene.***

<u>Registry Objective 2 (Cross-Sectional Phenotype Characterization)</u>

- **Registry Objective 2** is to characterize cross-sectional retinal dystrophy associated with disease-causing genetic variants using functional and structural measures (visual acuity, OCT, static perimetry), **<u>within-gene</u>**. Structure-function relationships and risk factors for disease severity will also be explored **<u>within-gene</u>**.
    - The distribution of each cross-sectional outcome measure will be summarized (including tabulating categorically, as well as means, SDs, medians, quartiles, ranges; *where sample size 20 or more*).

- Scatterplots and Spearman correlation coefficients between cross-sectional outcome measures will be explored (*where sample size is 20 or more*)
- Possible risk factors (genotype, phenotype, environmental, and comorbidities) for cross-sectional outcome measures will be explored (*where sample size is 40 or more*).
    - Methods will include univariate and multivariate analysis of covariance (ANCOVA) models. A stepwise selection procedure will be used to build the final model. A threshold of $P<0.10$ will be used to add to the model, and a threshold of $P<0.05$ will be used to remain in the multivariate model. Linearity of continuous factors will be assessed, and possibly quadratic or cubic terms will be considered if non-linear.
    - Potential risk factors to evaluate include:
        - Phenotypic:
            - Clinical diagnosis (if applicable)
            - Duration of disease
            - Age of onset of initial vision symptoms
            - Gender
            - Race/ethnicity
            - Visual acuity
            - Lens Status (phakic/pseudophakic/aphakic)
        - Genotypic:
            - Characterizations of the variants
        - Environmental factors
            - Smoking status
            - Vitamin A use
            - Docosahexaenoic acid (DHA) use
            - Lutein use
- Variability of symmetry of left and right eye cross-sectional outcome measures will be evaluated by scatterplots. Bland-Altman plots of the inter-eye difference versus the mean value will be inspected and a linear regression model for the differences will be used to test whether the intercept (overall mean difference) and slope is 0. The plot will be inspected to evaluate whether variability between eyes changes with greater mean values. The intraclass correlation coefficient of the values and the within-person variance will be estimated.

9.2.2 Natural History Data Analysis

The following Natural History Study data analysis considerations focus on **NHS Objectives 1-3** (see section 1.3). ***Applicability of <u>within-gene</u> objectives will depend on <u>within-gene</u> sample size***

as noted below. <u>If less than 20,</u> limit primary objective to describing the cohort in the form of case histories. Objectives may still be explored depending on the needs for a specific gene.

<u>NHS Objective 1 (Natural History)</u>

- **NHS Objective 1** is to characterize the natural history of retinal degeneration associated with disease-causing genetic variants over 4 years, using functional, structural, and patient-reported outcome measure, **<u>within-gene</u>** (*where sample size 20 or more*).
    - <u>Analysis plan for functional and structural measures</u>: The distribution of each outcome at each visit will be summarized (including tabulating categorically, as well as means, SDs, medians, quartiles, ranges; both the absolute change and percent change will be evaluated, tests performed multiple times will be analyzed using average of all available tests). To determine the average annual rate of progression in the population for each outcome, a repeated measure least squares regression model will be fit using all available outcome data at baseline and all annual visits. Multiple imputation will be used to impute the outcome values for all missing time points (including participants who discontinue follow up prior to 48 months). Secondary analyses using binary definitions of outcome measures will also be explored in time to event analyses; Kaplan-Meier estimates with 95% confidence intervals will be calculated.
    - <u>Analysis plan for PRO measures</u>: The scoring of each questionnaire will be completed according to the procedures for each instrument and is detailed further in a separate statistical analysis plan. Baseline scores will be cross tabulated with categorical (severity of disease) versions of the outcome measures of interest at baseline. Changes in scores will be cross tabulated with binary (progression of disease) versions of the outcome measures of interest at the 24- and 48-month visits. A generalized linear model adjusted for baseline differences will be explored.

<u>NHS Objective 2 (Structure-Function Relationship)</u>

- **NHS Objective 2** is to explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with disease-causing genetic variants, **<u>within gene (</u>***where sample size 20 or more)***.**
    - <u>Analysis plan</u>: Scatterplots and Spearman correlation coefficients of changes in functional and structural outcome measures of progression from baseline to each visit will be evaluated.

<u>NHS Objective 3 (Risk Factors for Progression)</u>

- **NHS Objective 3** is to explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with disease-causing genetic variants, **<u>within-gene</u>** (*where sample size 40 or more*).
    - <u>Analysis plan</u>: The distribution of each outcome in terms of both absolute change and percent change from baseline to 4 years will be summarized (including tabulating categorically, as well as means, standard deviations,

medians, quartiles), stratified by categorical levels of each potential risk factor of interest (listed below). Potential risk factors to evaluate include:

- Phenotypic:
  - Clinical diagnosis (if applicable)
  - Duration of disease
  - Age of onset of initial vision symptoms
  - Gender
  - Race/ethnicity
  - Visual Acuity
  - Lens Status (phakic/pseudophakic/aphakic)
- Genotypic:
  - Characterizations of the variants
- Environmental factors
  - Smoking status at baseline
  - Vitamin A use at baseline
  - Docosahexaenoic acid (DHA) use at baseline
  - Lutein use at baseline

Other Planned Analyses

- Analysis plan for variability of repeat perimetry testing at baseline: Scatterplots and Spearman correlation coefficients for pairs (first versus second) of testing values for each repeated perimetry test. Bland-Altman plots of difference versus the mean value will be inspected. The intraclass correlation coefficient of the values and the within-eye variance will be estimated.
- Analysis plan for the symmetry of left eye versus right eye: At baseline and each subsequent testing time, the symmetry of the test result values from the left and right eyes will be assessed and the symmetry of the change from baseline from the left and right eyes will be assessed for each follow-up visit. Bland-Altman plots of the inter-eye difference versus the mean value will be inspected. The intraclass correlation coefficient of the values will be estimated.

9.2.3 Interim Data Analysis

No formal interim analysis or "stopping guidelines" are planned for determining early stopping according to statistical rules, as no intervention is being studied and thus early efficacy and safety signals are not applicable.

Interim analyses will be planned for other reasons, including to evaluate data at baseline and annual visits for reporting in preliminary manuscripts, as well as monitoring data for recruitment and retention benchmarks, and quality assurance throughout the duration of the study. The FFB Consortium Executive Committee will review and oversee these data and their use in reporting.

Chapter 10: Data Collection and Monitoring

10.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. **This source must be readily verifiable against the values entered into eCRF.** Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.) and provided to the coordinating center for review.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 and regulatory and institutional requirements for the protection of confidentiality of participants

10.1.1 Central Genetics Auditor (CGA)

The CGA will review the genetic lab report(s) submitted by the clinical site during genetic screening and will document their verification of these genetic data on the FFB Consortium study website.

10.1.2 Genetics Committee (GC)

In addition to providing assistance in the interpretation/evaluation of whether the mutations are causative of the disease on the FFB Consortium study website, the Genetics Committee will review and provide approval for the use of genetic reports from research labs to be used for determining participant eligibility.

10.1.3 Reading Center (RC)

Reading Centers will conduct grading of the study data collected using the FFB Consortium study website. The Reading Centers will provide the graded data through a data transfer or by entering the graded data on the study website. These data will remain in the study database and will not be provided to the clinical site.

10.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents will be retained for a minimum of six (6) years from the date on which the CC receives IRB approval to close the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Principal Investigator (PI) when these documents no longer need to be retained.

10.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).[9] Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 312.[10] This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the Investigator(s), or the study site staff.

A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to the study participants, adversely affects the welfare, rights, or safety of the research study participants, or negatively influences the scientific study integrity. As a result of significant deviations, corrective and preventive actions are to be developed by the site and implemented promptly.

The site Principal Investigator (PI) and study staff are responsible for knowing and adhering to their IRB/EC requirements.

Chapter 11: Ethics/Protection of Human Participants

11.1 Ethical Standard

The Principal Investigator (PI) will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research in accordance with ICF E6/GCP, EC requirements, and local laws and regulations, as applicable.

11.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB/EC-approved, and the participant will be asked to read and review the document. The Investigator(s) will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating Investigator(s), their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover use of genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/EC, regulatory agencies or company supplying study product may inspect all documents

and records required to be maintained by the Principal Investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the FFB Consortium Coordinating Center, located at the Jaeb Center for Health Research in Tampa, FL. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the FFB Consortium Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the FFB Consortium Coordinating Center.

11.3.3 Future Use of Data and Ocular Images

Data and images collected for this study will be analyzed and stored at the FFB Coordinating Center and the Reading Centers. After the study is completed, the de-identified, archived data will be transmitted to and stored at the FFB Consortium Coordinating Center, under the supervision of the Protocol Director, for use by other researchers including those outside of the study. Permission to transmit data to the FFB Consortium Coordinating Center will be included in the informed consent.

Chapter 12: References

References

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