Uni-Rare Study

JOSÉ-ALAIN SAHEL

Ocular Disease Forum
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Disclosures

Jose-Alain Sahel is a co-founder of

Pixium Vision, GenSight Biologics, Prophesee, Tilak Healthcare, Chronolife, Sparing Vision, Avista Rx, Vegavect, Tenpoint, Cilensee, SharpEye

He is a paid consultant for Tenpoint and Avista Rx

He is a member of the SAB of Foundation Fighting Blindness, the Gilbert Family Foundation, The Institute of Ophthalmology of Basel

Funding

The Uni-Rare protocol is funded by the Foundation Fighting Blindness (FFB). The Natural History Study (NHS) for selected genes may be funded by other sources.

Importance of Natural History Studies (NHS)

- Despite progress in therapy development, and a growing number of interventional trials for IRDs, there remain significant hurdles to designing trials and advancing therapies
- Recent papers have reviewed unmet needs and identified top priorities to move the promise of IRD treatment forward

  Common theme: the vital need for natural history studies

Duncan et al. 2018; Thompson et al. 2020; Csaky et al. 2017

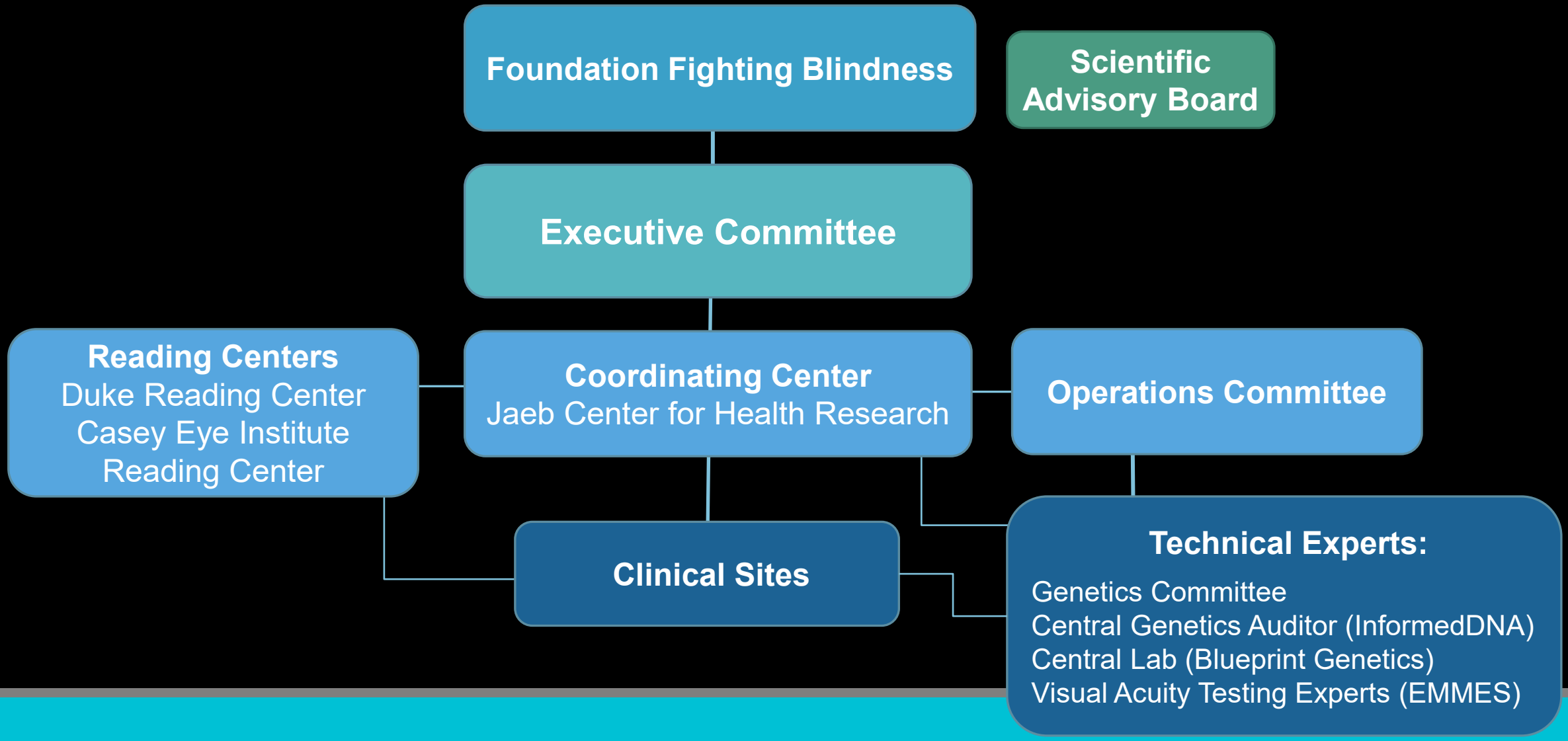
- In 2016, FFB initiated an international Consortium of clinical centers to conduct IRD research
- Goal: Accelerate development of treatments for IRDs
- Based on the Diabetic Retinopathy Clinical Research Retina Network model

FOUNDATION FIGHTING BLINDNESS
CONSORTIUM

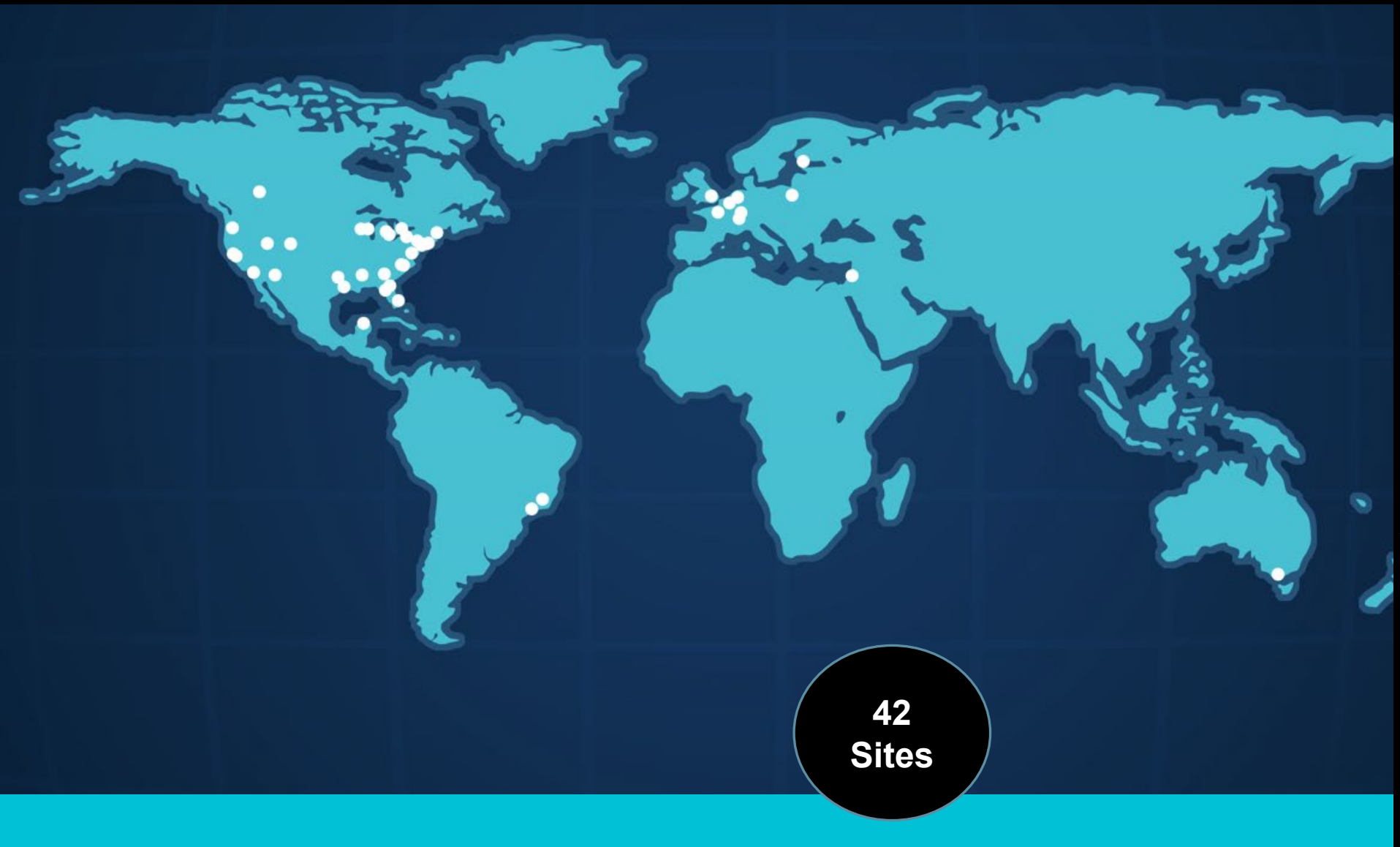
FFB Consortium Model

- Investigators collaborate on ideas for hypotheses, study designs, and publications
- Consortium natural history studies:
  - Provide prospective long-term natural history data about disease onset and progression
  - Identify sensitive structural and functional outcome measures for clinical trials
- Data from completed studies will be archived in an open central repository to stimulate further hypothesis generation and innovation

FFB Consortium Organizational Structure



FFB Consortium Clinical Sites



University of Michigan, Kellogg Eye Center
OHSU, Casey Eye Institute
Cincinnati Eye Institute
Columbia University
Baylor College of Medicine, Alkek Eye Center
Emory University, Emory Eye Center
Ghent University
Harvard University, MEE
Medical College of Wisconsin Eye Institute
Moorfields Eye Hospital
National Eye Institute
CHNO des Quinze-Vingts
Radboud University Medical Center
Retina Foundation of the Southwest
Rutgers University
University of California San Francisco
University of Toronto, Hospital for Sick Children
University of Tuebingen, Centre for Ophthalmology
University of Utah, John Moran Eye Center
Vitreo Retinal Associates
Johns Hopkins University, Wilmer Eye Institute
Duke University, Duke Eye Center
Colorado Retina Associates
University of Arkansas, Jones Eye Institute
University of North Carolina, Kittner Eye Center
Medical University of Lublin
Stanford University, Byers Eye Institute
University of Miami, Bascom Palmer Eye Institute
University of Wisconsin Madison
Associated Retina Consultants
UCSD, Jacobs Retina Center
Helsinki University Hospital
Hadassah-Hebrew University Medical Center
UPMC Eye Center
Federal University of São Paulo
University of Pennsylvania, CAROT
INRET Clinica e Centro de Pesquisa
University Hospital of Basel
University of Alberta
Instituto de Retina
University of Florida
University of Melbourne

FFB Consortium Natural History Studies to Date

Study	Details
#1 - Rate of Progression in *USH2A*-related Retinal Degeneration (RUSH2A)	Study Chair: Jacque Duncan, MD Final Sample Size: 127 participants Status: 4-yr follow-up to be completed December 2022
#2 - Rate of Progression in *EYS*-related Retinal Degeneration (Pro-EYS)	Study Chair: Mark Pennesi, MD, PhD Final Sample Size: 103 participants Status: 4-yr follow-up to be completed December 2025
#3 - Rate of Progression of PCDH15-related Retinal Degeneration in Usher Syndrome 1F (RUSH1F)*	Study Chair: Katarina Stingl, MD Sample Size Goal: 45 participants Status: Recruitment to be completed 2022, 4-yr follow-up to be completed 2026
#4 – Gyrate Atrophy Ocular and Systemic Study (GYROS)†	Study Co-Chairs: Mandeep Singh, MD and David Valle, MD Sample Size Goal: 45 participants Status: Recruitment to be completed 2024, 4-yr follow-up to be completed 2028

***Co-funded by FFB, Usher 1F Collaborative & Marjorie C. Adams Foundation**

†Co-funded by FFB, Conquering Gyrate Atrophy, and FDA -- *This project is supported by the FDA of the U.S. Department of HHS as part of a financial assistance award R01FD007628 totaling $1.6M with 42 percentage funded by FDA/HHS and $2.2M amount and 58 percentage funded by non-government sources. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government*

Objectives of our Natural History Studies

- Estimate rates of progression
- Investigate structure-function relationships
- Explore candidate endpoints (including signal-to-noise, reproducibility, symmetry)
- Identify factors related to progression
- Define genotype-phenotype associations
- Provide a source of historical control data
- Inform the design and practical challenges of clinical trials

Outcome Measures in our Natural History Studies

- Structural outcome measures
  - Spectral-domain optical coherence tomography EZ area, fundus autofluorescence
- Functional outcome measures
  - Static perimetry, microperimetry, full-field stimulus threshold, electroretinography, visual acuity, contrast sensitivity, color vision
- Structure-function relationships
  - Static Perimetry-optical coherence tomography overlay, Microperimetry-optical coherence tomography overlay
- Patient-reported outcome measures
  - Visual function questionnaires and quality-of-life questionnaires

Background

- **Problem:** Individual natural history studies for each rare IRD gene not feasible or efficient
  - Large expense per study regardless of the number of pts
  - Considerable startup time for site certification (contracts, IRB/ethics, etc)
  - Many sites have just 1-2 pts for a particular gene, cannot justify the effort to participate in a study
- **Solution:** Design a **universal protocol** for all rare IRD genes

Universal Rare Gene Study (Uni-Rare)

- **Study Chair:** José-Alain Sahel, MD
- **Registry Component**
  - Prospective, standardized, cross-sectional clinical data collection
  - Open to >300 rare IRD genes
  - N=1500

→ Genotype Characterization
Cross-Sectional Phenotype Characterization

- **Natural History Study (NHS) Component**
  - Prospective, standardized, longitudinal (4 years) clinical data collection
  - A platform to move participants from the registry as each gene opens
  - N=100 cap per gene

→ Natural History using Functional, Structural, PRO Measures
Structure-Function Relationship
Risk Factors for Progression

Uni-Rare Impact

Part 1 – Prospective, cross-sectional registry

Establish genetically and clinically well-characterized cohorts across hundreds of genetic variants associated with retinal dystrophy. Characterization of these patients will:

- **Provide cross-sectional data on phenotype-genotype associations**
- **Contribute to our knowledge of pathogenicity of these rare disease-causing variants**
- **Accelerate eligibility screening for subsequent natural history studies**

Uni-Rare Impact

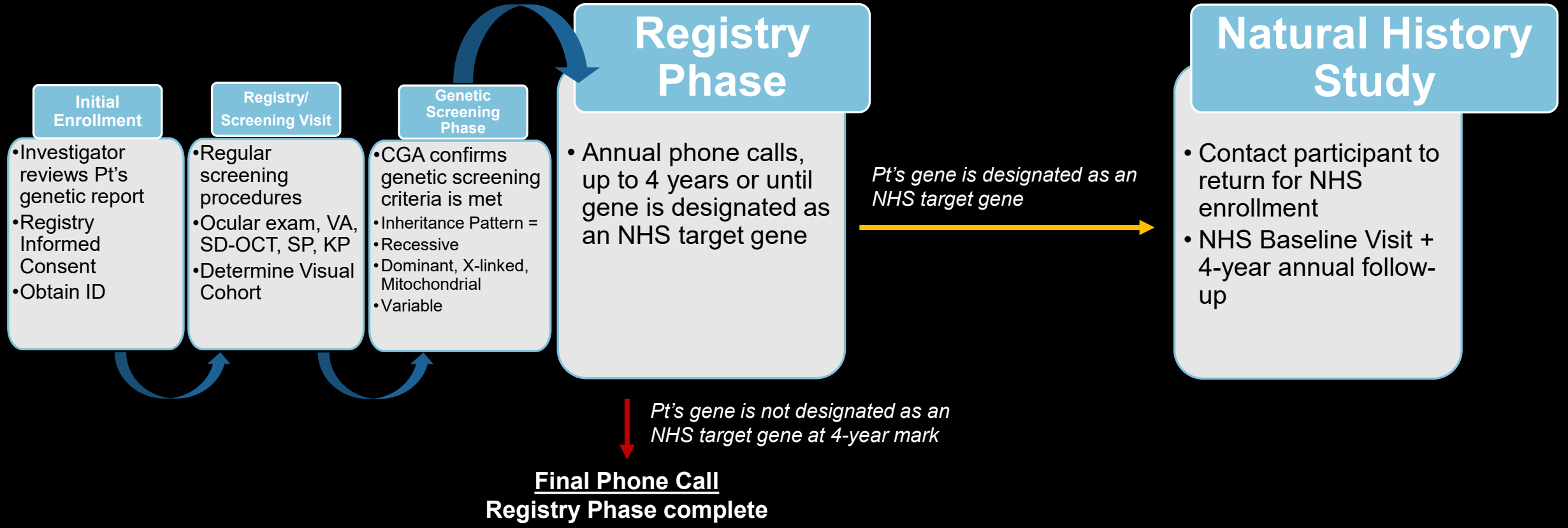
Part 2 – Prospective, natural history

Accelerate identification 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 to:

- **Describe the natural history of retinal degeneration in patients with rare disease-causing genetic variants**
- **Define sensitive structural and functional outcome measures for future multicenter clinical trials of rare inherited retinal degeneration**
- **Identify well-defined subpopulations for future clinical trials of treatments for rare inherited retinal degeneration**

Study Design

Participant Flow Overview



Study Design

Key Eligibility Criteria

- Age ≥ 4 years
- Clinical diagnosis of retinal dystrophy
- Must meet Genetic Screening Criteria
  - Genetic testing must already be done outside the study

Study Design
Registry Testing Procedures

Procedure	Details
Collect MyRetinaTrackerID	If participating and consent to provide
Demographics	Race, ethnicity, gender
Medical History	Pre-existing conditions, symptomology history, medications
Genetic Screening Criteria Assessment	See protocol definition
Ophthalmic Exam	Can be historical - within last 6 months
Visual Acuity (EVA or ETDRS/HOTV charts) + LLVA/BRVT	**Consortium-certified technicians and procedures**
SD-OCT (Heidelberg Spectralis)	**Consortium-certified technicians and procedures**
Static Perimetry (Octopus 900 Pro)	**Consortium-certified technicians and procedures**
Kinetic VF III4e (for Vision Cohort definition)	Can be historical - within last 18 months

Study Design

NHS Visits and Testing Procedures

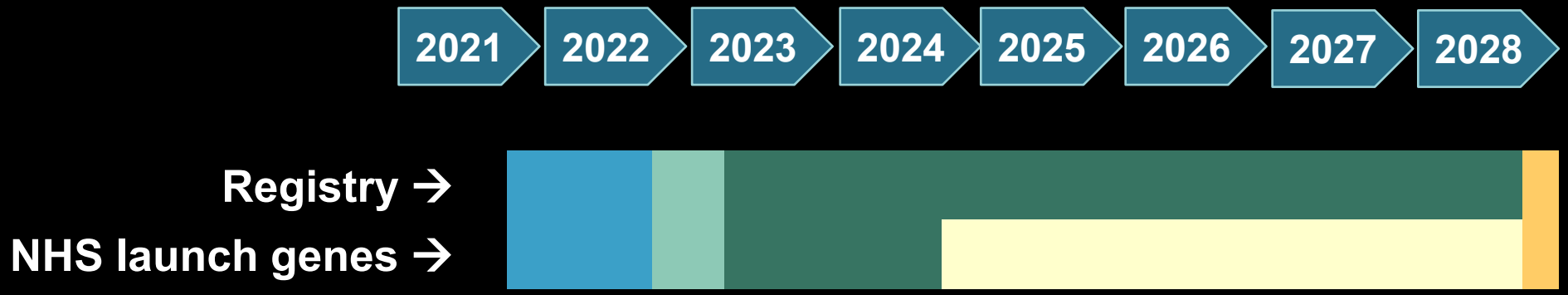
	BL	12M*	24M*	36M*	48M
Medications/AEs/Medical Hx	X	X	X	X	X
Patient Reported Outcomes	X		X		X
Ophthalmic Exam	X	X	X	X	X
Visual Acuity (EVA or ETDRS/HOTV charts) + LLVA/BRVT	X	X	X	X	X
Color Vision (Lanthony D15)*	X	X	X	X	X
Contrast Sensitivity (CSV-1000E)*	X	X	X	X	X
SD-OCT (Heidelberg Spectralis)	X	X	X	X	X
Axial Length**	X				
Color Photo (Optos)	X				
Fundus Autofluorescence (Optos)	X	X	X	X	X
Full-field ERG (Diagnosys Espion)*	X				X
Full-field Stimulus Threshold (Diagnosys Espion)	X	X	X	X	X
Static Perimetry (Octopus 900 Pro)*	X†	X	X	X	X
Fundus-guided Microperimetry (MAIA)*	X†	X	X	X	X

* Visits/tests not required for Vision Cohort 3

** Axial Length will be performed at every visit for pts <18 years old at baseline.

† Up to 3x at Baseline

Uni-Rare Study Timelines



- Goal for Registry Recruitment (current funding)
  - N = 1500 in 18 months
  - Each site enrolls ~4 per month (ramp up to 30 certified sites)
- Goal for NHS launch genes (RDH12, MYO7A, [few more TBD])
  - N = anticipate up to 180 to be enrolled in 18 months

Uni-Rare Long-Term

- **Strategy:** Initial Uni-Rare launch will allow us to
  - Set up the infrastructure
  - Be positioned to easily add new genes with new funds
  - Attract funding partners
- **Impact:** Uni-Rare will provide the foundation to reduce costs and accelerate timelines, while leveraging strength in numbers and standardized data collection in very rare genes otherwise overlooked due to these hurdles
- **Significance:** Uni-Rare provides inclusivity (all patients are eligible/all centers can contribute using the same standards)

Uni-Rare Efficiencies

Study elements designed to be truly universal when adding new NHS genes	
Protocol	No amendment needed – JCHR IRB will allow a simple notification
Consent	One Registry consent One universal NHS consent
Contract Agreement	Standard set of visit-based payments
Site/Inv/Coord Certification	One set of protocol training/documentation requirements

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No need to "rebuild the stadium" each time

Thank you