

Tackling the Challenges of Product Development Through a Collaborative Rare Disease Network: The Foundation Fighting Blindness Consortium

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The Foundation Fighting Blindness, a 501(c)(3) nonprofit organization, established an international consortium of inherited retinal disease specialists in 2016, with a mission to accelerate the development of treatments for rare, inherited retinal degenerations, such as retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis, Usher syndrome, choroideremia, and achromatopsia. The Consortium accomplishes its mission by evaluating novel outcome measures, sharing standardized study protocols and datasets, and disseminating findings. Having established research infrastructure in the first 3 years, including 39 global research sites, the network is now poised to expand its infrastructure for trials of new therapies in partnership with industry. This model represents an innovative approach to overcome challenges of therapeutic development for rare diseases.

Introduction

Recently, in response to a Request for Information from the US Food and Drug Administration, we shared our experience building a rare disease clinical trial network (<https://beta.regulations.gov/document/FDA-2020-N-0837-0027>). We thought the readers of *TVST* would be interested in how a rare disease clinical trial network can bring together clinical experts and inform industry partners to address the challenges encountered when developing therapies for rare diseases.

The Foundation Fighting Blindness (the Foundation) is a 501(c)(3) nonprofit organization established in 1971 with a mission to accelerate the development of treatments and cures for inherited retinal degenerations (IRDs), including retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis, Usher syndrome, choroideremia, achromatopsia, and others. These conditions are associated with a significant economic burden owing to decreased workforce participation and loss of well-being.¹ As a group, these rare IRDs affect approximately 4.5 to 6.8 million people worldwide and 200,000 to 300,000 Americans. Thus, each of the rare IRDs meets the US Food and Drug Administration's definition of an orphan disease. The term "rare IRD" is a convenient, but misleading, label to describe a collection of heterogeneous diseases. They are genetically diverse (>270 causative genes have been identified to date) and have vastly different clinical manifestations in terms of age of onset, severity of disease, rate of progression, and patterns of anatomic and functional abnormalities. Understanding this phenotypic heterogeneity poses an important challenge for therapy developers. To be successful, they must identify suitable outcome measures and match them with their therapeutic strategy (including delivery to the appropriate retinal cell types) and the therapeutic goal (e.g., slowing progression or improving vision).² The variety of promising treatment approaches is evident in the current therapeutic pipeline, ranging broadly from gene editing and augmentation for early stage disease; to neuroprotection for midstage disease; and to prosthetics, optogenetics, and cell therapy to restore some light sensation in late-stage disease.^{3,4}

The Foundation's program of sponsored clinical studies began in 2010. It has led to the development of novel outcome measures and added greatly to our understanding of IRDs. The first study, a randomized clinical trial of valproic acid (NCT01233609) in individuals with autosomal dominant retinitis pigmentosa failed to demonstrate a treatment benefit, but was the basis for research that identified the area of

the ellipsoid zone (intact photoreceptors), estimated from optical coherence tomography, as a sensitive and reliable outcome measure in retinitis pigmentosa.^{5,6} Numerous outcome measures in Stargardt disease have been characterized from our second study, ProgStar (NCT01977846).⁷⁻¹⁰ The scientific output from this study, in the form of 22 publications and numerous downloads of study datasets, has generated significant industry interest and pointed the way to our most recent framework for collaborative clinical research.

To extend the success of our early clinical studies, the Foundation established an international consortium of IRD specialists in 2016 (<https://public.jaeb.org/ffb>), whose mission is to accelerate the development of treatments for IRDs. The Consortium is developing centers of excellence to participate in sponsored clinical studies that generate robust and high-quality data using standardized protocols.⁴ Investigators from participating clinical centers collaborate to assess risk factors and develop outcome variables from prospective natural history studies of IRDs, using standardized protocols. Using this information, the Consortium focuses on clinical trial development, including the development of hypotheses, creating study protocols, carrying out clinical trials, analyzing the data and publishing the results. As part of the Consortium's mission to stimulate further hypothesis generation and innovation, de-identified datasets will be archived in a central repository after study completion, and readily available to other researchers via a data transfer and processing agreement. Currently, the Consortium has 39 sites (28 in the United States) in 11 countries across North America, South America, Western Europe, and the Middle East. In addition to the sites, the research infrastructure includes a coordinating center, reading centers, technical experts, and oversight committees. All of these components have been developed through our experience launching 2 large multicenter natural history studies, Rate of Progression in *USH2A*-related Retinal Degeneration (RUSH2A; NCT03146078) and Rate of Progression in *EYS*-related Retinal Degeneration (Pro-EYS; NCT04127006).

Recruitment for RUSH2A and Pro-EYS has been aided by the Foundation's My Retina Tracker Registry and its associated genetic testing program.¹¹ The registry is open to individuals with IRDs (or their caregivers) who complete survey modules that cover their diagnosis, family history, diagnostic journey, current vision, and overall health. This information, in conjunction with genetic test results, enables the Foundation's registry staff to identify and contact registry members who may be candidates for clinical studies.

Now in our fourth year and with critical infrastructure in place to support treatment trials, the Consortium has begun to focus on three inter-dependent objectives. First, we aim to ensure we are productive and impactful by soliciting research ideas from our investigators and others, prioritizing work to develop novel outcome measures, and disseminating our findings. Second, we are focused on improving cost, efficiency, and quality because we have an obligation to donors who fund our work and because economics play a large role in determining whether sites can participate in research studies. Third, we are building avenues toward sustainability, which we view in terms of investigator engagement and project cofunding. We envision mutually beneficial partnerships of many forms, including early access to study datasets, joint development of novel outcome measures, and leveraging our entire research infrastructure to conduct clinical trials of novel treatments. Whatever form our partnerships take, the Consortium will remain open and flexible to conduct clinical trials of promising new therapies, even if they have not yet attracted industry funding.

We have evolved over time in response to numerous challenges related to economics (e.g., ensuring site budgets are at least cost-neutral), site participation and engagement, coordination of international sites (such as translation of patient documents), the needs of industry partners (e.g., early access to data, concerns with study timelines), and novel coronavirus disease 2019 research disruptions. Although these challenges have been significant, we are frequently reminded of another inherent challenge that rare disease networks need to address. Many rare diseases do not have well-established clinical outcome measures,⁴ and, as in our case, it is an explicit goal of the network to develop relevant outcome measures, including patient-reported outcomes or performance-based tests to assess disease impacts. However, these innovations require significant investment in standardizing protocols suitable for multicenter studies, developing training and certification processes, aligning investigators as to the importance of the resource-intensive work, strategic partnering with industry, and feedback from patients. We strive to not only collect data from patients in an efficient manner, but also to explore optimal methods to analyze the data.

We believe these efforts will pay tremendous dividends. Careful follow-up of well-characterized cohorts with rare diseases fills knowledge gaps about anatomy, function, social determinants of health, and disease impacts. These data can be useful to identify individuals who are most likely to benefit from a new therapy and, therefore, facilitate the design and

enrollment of clinical trials. The eventual success of new therapies in clinical trials also depends on having valid and reliable outcome measures. These tools are being developed by the scientific and clinical experts in our network and shared with the greater research community, thus removing development uncertainty and paving the way for the accelerated development of valuable new therapies.

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* For a list of participating clinical centers, see the FFB Consortium public website (<https://public.jaeb.org/ffb>).

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