CASE STUDY

CRITICAL PATH INSTITUTE

Friedreich's Ataxia Integrated Clinical Database: **Regulatory-Grade Evidence for a Rare Disease**

PROBLEM

Friedreich's ataxia (FA) is an inherited, progressive, and life-shortening neurodegenerative disease that affects approximately 5,000 people in the United States and 22,000 worldwide, and for decades it had no approved treatment.[2] Developing therapies for FA runs into the defining problem of rare disease research: patient populations are small and geographically dispersed, disease progression varies widely between individuals, validated endpoints are limited, and commercial investment is scarce.

These constraints make large, long randomized controlled trials difficult to enroll and complete, and they make modest changes in clinical scores hard to distinguish from the natural course of the disease. Meaningful data existed, but it sat fragmented across sponsors and studies, collected in inconsistent formats, and was not readily usable for regulatory decision-making. The unavoidable question for any sponsor was how to show that an observed treatment effect reflected durable clinical benefit rather than statistical noise.

SOLUTION

Critical Path Institute® (C-Path), an independent nonprofit established in 2005 as a public-private partnership in response to the FDA's Critical Path Initiative, partnered with the Friedreich's Ataxia Research Alliance (FARA) to build a shared, regulatory-grade data foundation for the disease. FARA had funded and built FA-COMS, the Friedreich's Ataxia Clinical Outcome Measures Study, a global, multi-center, prospective natural history study that has followed patients annually since 2003 on the modified Friedreich's Ataxia Rating Scale (mFARS) and other measures.[8,9]

In 2019, the two organizations launched the Friedreich's Ataxia Integrated Clinical Database (FA-ICD), consolidating de-identified, patient-level data from multiple industry clinical trials together with the FA-COMS natural history data into a single standardized resource.[5] C-Path's Data Collaboration Center mapped all contributed data to Clinical Data Interchange Standards Consortium (CDISC) standards, curated and quality-checked it to regulatory-grade quality, and managed patient privacy and controlled access. The datasets were later consolidated into C-Path's Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) for stronger security and integrated analytics.[6]

The integrated evidence base

DATA ASSET	TYPE	ROLE IN THE EVIDENCE BASE
FA-COMS natural history study	Prospective, multi-center natural history	Longitudinal mFARS trajectories; the source of matched external-control comparators
Industry clinical trial datasets	Interventional trial data	Standardized trial outcomes enabling cross-study comparison and analysis
FA-CHILD study	Pediatric natural history	Extends progression data to younger patients
CDISC standards and RDCA-DAP hosting	Data standards and platform	Makes the data comparable, secure, and reusable for regulatory analysis

Approach: a natural history external control

Standardization made the FA-COMS data usable as an external control, so a treated cohort could be measured against well-characterized, matched patients rather than a concurrent placebo group. In the analysis that supported approval, each patient in the open-label extension of the MOXIe trial of omaveloxolone was matched to a similar FA-COMS patient on characteristics including sex, age, age at disease onset, and baseline severity.[1]

COHORT	PATIENTS (n)	3-YEAR mFARS CHANGE	INTERPRETATION
Matched natural history (FA-COMS)	136	+6.61 points	Faster progression
Omaveloxolone (MOXIe extension)	136	+3.00 points	Slower progression
Difference	n/a	**−3.61 points**	About 55% slower progression, favoring treatment

On the mFARS, scores range from 0 to 93 and higher scores indicate greater impairment, so an increase reflects disease progression. The difference was statistically significant (nominal p = 0.0001).[1]

IMPACT

This external-control evidence complemented the randomized MOXIe Part 2 result, a 2.4-point placebo-corrected benefit on the mFARS at 48 weeks, and together they formed the totality of evidence the FDA reviewed.[1,2] On February 28, 2023, the FDA approved SKYCLARYS (omaveloxolone) as the first treatment ever approved for Friedreich's ataxia.[4]

The infrastructure has since expanded. FA-COMS now spans more than 20 years of follow-up and 1,450 patients across the United States, Canada, Australia, New Zealand, and India, with pediatric data from FA-CHILD, all hosted in RDCA-DAP.[6,7] The integrated data now supports disease progression models and a clinical trial simulation tool in development, intended to help design and interpret future FA trials.

Advantages of standardized, regulatory-grade natural history data

The primary value of this work is a reusable evidence foundation that does not expire with a single approval. Standardization converts scattered patient records into data a regulator can act on. A well-matched external control gives reviewers the context to judge whether an effect is durable when a full-scale placebo-controlled trial is not feasible in a small, variable population. And because the platform, standards, and models persist, each new dataset strengthens the base available for the next trial, the next external control, and the next submission.

Key takeaways

1. When randomized evidence is constrained, high-quality standardized natural history data can materially strengthen an approval package.
2. Data standards are a strategic asset, not administrative overhead. CDISC mapping and disciplined curation are what made the data usable for regulatory review.
3. Cross-sector collaboration de-risks rare disease development. A patient foundation, a nonprofit data organization, industry sponsors, and the FDA each contributed a capability none held alone.
4. The infrastructure outlasts the milestone. The same platform, now enriched with pediatric data and progression models, is a durable foundation for future FA drug development.