THE FA GCC GLOBAL CLINICAL CONSORTIUM

MARCH 2024 NEWSLETTER

TABLE OF CONTENTS

FARA Friedreich's Ataxia Research Alliance

THE
FA GCC
GLOBAL CLINICAL CONSORTIUM

FA GCC Site Spotlight

In each newsletter, we will spotlight an FA GCC site and introduce you to their team. If you're interested in spotlighting your team, please email a group photo(s) and a short introduction or Q&A to fagcc-info@curefa.org.

Our first spotlight is an introduction to the FARA FA GCC team.

Cait Monette:

What got you interested in FA research? My cousin was diagnosed with FA when I was in grade school, which sparked my interest in genetics, Friedreich's ataxia, and, ultimately, lead to my career in clinical research.

Jen Farmer:

What's been the highlight of participating in the FA GCC for you so far? The best part of the FA GCC is that it engages all FA community stakeholders and has a direct and tangible impact on our ability to accelerate the development of treatments for FA. The FA GCC engages: dedicated FA clinicians and researchers to lead the scientific agenda and carryout the research studies; individuals and families with FA to volunteer for research studies and contribute their data and experience living with FA; donors and supporters to ensure we have funding for the natural history study and other research; biotech and pharma partners committed to developing therapies and other advocacy partners to facilitate and amplify all efforts of the FA GCC.

Myriam Rai:

What got you interested in FA research? My journey in FA started with Massimo Pandolfo. After spending an hour in his office, I remember leaving with the original reprint of the Science paper describing the GAA repeat expansion in FA. The next morning I decided to go for a PhD on FA. I was quickly introduced to the FA community: scientists, clinicians, advocacies, and, of course, persons living with FA.

Left to right. **Members of the FA GCC management team in blue.**
Top: Erin Goers - Database Manager/ Development Associate, Felicia Derosa - Vice President Fundraising and Communications, **Jennifer Farmer - Chief Executive Officer, Cait Monette - Director of Clinical Operations,** Maureen Juip - Secretary / Director
Middle: **Myriam Rai - Director of Global Relations & Initiatives**, Layne Lavicky (Rodden) - Former Director of Patient Engagement and Postdoctoral Research Fellow at Baylor College of Medicine, Naseem Baksh - Administrative & Program Assistant, Ron Bartek- President/Director/Co-Founder, Jamie Dean - Director of Operations and Special Projects Front: Kyle Brant - rideATAXIA Founder & Director

FARA Friedreich's Ataxia Research Alliance

Workgroup Updates

Cardiac Natural History workgroup highlights the importance of prospective cardiac data collection under UNIFAI. This group is encouraging all sites to enter the Cardiac Event, Holter Monitor, ECHO, and EKG forms whenever available. Reimbursement for the data entry of these ancillary cardiac collection forms is available under the new UNIFAI contracts at a rate per form.

Pediatric and Presymptomatic workgroup (pictured below) has picked up action items from the pediatric workshop. The investigators are collecting information on existing mFARS normative data in control children and are investigating home-based remote measurements (digital data).

Patient Advisory Team (PAT) workgroup will meet in Q2 to get started and select a representative to attend the Steering Committee meetings.

Bio-sample workgroup is leading an initiative to create a central listing of the FA samples available at each site for consortium collaborative research projects. This listing will be kept at a central location allowing FA GCC Investigators with a project in mind to easily collaborate with other members who have existing bio-samples of interest.

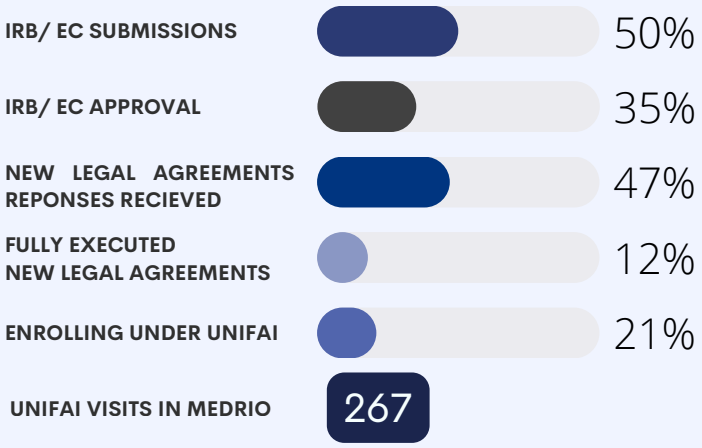
Cognition and Mood workgroup is excited to leverage learnings from the baseline analysis of cognition and mood questionnaires (CCAS, RCADS, and HHADS) collected under the TRACK FA study. The group continues to develop a protocol for an in-depth neuropsychological test battery. This battery will be administered along with neuropsychiatric questionnaires and social cognition tests to a subset of participants.

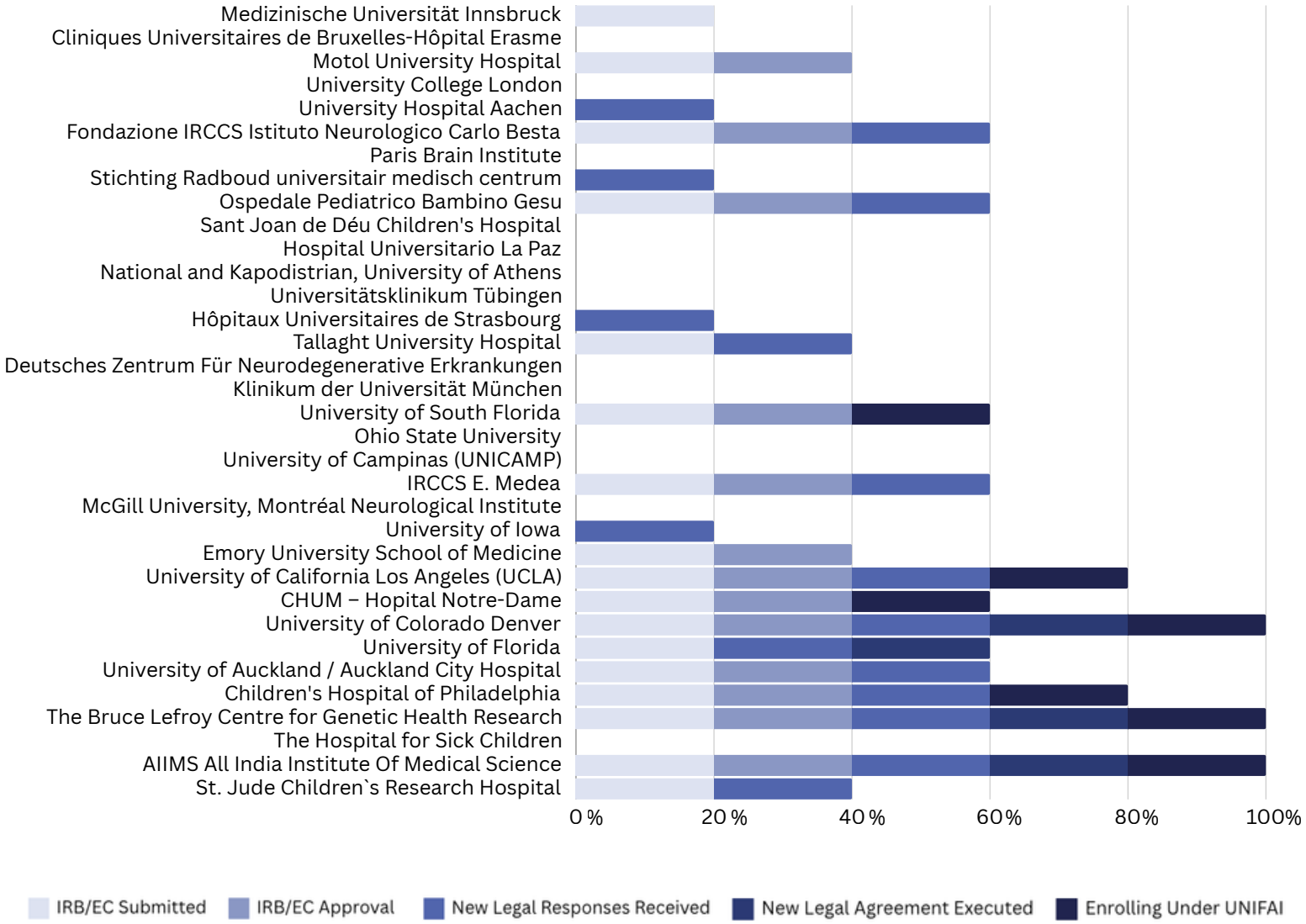
Late Stage Symptom workgroup is generating a standardized virtual visit guideline to follow when UNIFAI visits need to take place remotely. The group is also looking into measures of late-stage ADLs, social interaction, speech, hearing, and alternative modes of communication.

FA GCC Mission Statement: Accelerate the development of treatments for Friedreich's Ataxia by empowering patients and researchers, understanding natural history, conducting research and developing infrastructure that facilitates clinical research across the globe.

Site Transition Status

Sites continue the transition to the UNIFAI study. **Fifty percent of global sites** have submitted the harmonized UNIFAI protocol to their ethics committee (EC)/IRB as of February 29, 2024.





Process for Proposal to FA GCC

The Medrio EDC Infrastructure set up by the FA GCC to support UNIFAI is also available as a resource for the collection of ancillary assessment data and sub-study data. Please keep this opportunity in mind for upcoming projects.

A link to the forms for submitting a project or sub-study to the Steering Committee can be found below.

Appendix A - Proposing a project or sub-analyses of consortium data to the FA GC Steering Committee
Appendix B - Proposing a Study or Sub-Protocol to the FA GC Steering Committee

CLICK TO DOWNLOAD

PHARMA NEWS

Biogen Receives European Commission Approval for SKYCLARYS® (omaveloxolone)

Biogen Inc. announced the European Commission has authorized SKYCLARYS® (omaveloxolone) for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. SKYCLARYS is the first treatment approved within the European Union for this rare, genetic, progressive neurodegenerative disease.
Click here to read the full press release. Biogen Received European Commission Approval for SKYCLARYS® (omaveloxolone), the First Therapy to Treat Friedreich's Ataxia | Biogen

Larimar Therapeutics Reports Positive Top-line Data from Phase 2 Dose Exploration Study from 25 mg and 50 mg Cohorts of Nomlabofusp in Patients with Friedreich's Ataxia

Larimar Therapeutics, Inc. announced positive top-line data and successful completion of its four-week, placebo-controlled Phase 2 dose exploration study of nomlabofusp (CTI-1601) in participants with Friedreich's ataxia. Nomlabofusp was generally well tolerated and demonstrated dose dependent increases in frataxin levels in all evaluated tissues (skin and buccal cells) after daily dosing of 14 days followed by every other day dosing until day 28 in the 25 mg and 50 mg cohorts.
Click here to read the full press release.

UNIFAI Study - Frequently Asked Questions (FAQ)s

Q: Should my site complete all ancillary assessments?

A: No, 2-3 ancillary assessments will likely fit during a visit. Ancillary/optional assessments may be specific to a subgroup of patients (pediatric) or site's capabilities and equipment. Ancillary assessments are to be used selectively and in a manner that will allow for useful analysis (consistently).

Q: What assessments are required to make an in-clinic visit qualify as payable?

A: Each site should collect or attempt all required/core assessments – FA ADL, Ataxia Scale (mFARS and/or SARA), FDS, 9HPT, T25FW/8MW, SF36/SF10, and EQ5D.

Q: How will UNIFAI participant IDs be generated?

A: *New enrollment participants:* The participant must be registered in the Medrio EDC system, and then the system will automatically generate the next sequential ID number; this number will be unique study-wide.
FACOMS existing participants: migrated from FACOMS will keep their same study numbers.
EFACTS existing participants: migrated from EFACTS will be assigned a placeholder ID; when your site is ready to enter data under UNIFAI, a code list connecting the EFACTS ID to the new UNIFAI ID will be provided from Claire Didszun.

Q: Is there a central location to find other related resources?

A: Yes – UNIFAI resources can be found by clicking on the "UNIFAI" tab, then the "View Study Documents" link in Medrio. These resources currently include the UNIFAI Study Database Manual and a list of the site contacts for other UNIFAI sites. Please reach out to fagcc-info@curefa.org if you need updates made to the contact information for your site.

Q: Do participants still need to be re-consented annually?

A: There is no longer a requirement from the FA GCC to re-consent participants annually, unless this is a requirement from your local IRB/EC. Participants will be reconsented when there are relevant updates or changes to the study.

Recent Publications

FA GCC member Elisabetta Indelicato from Innsbruck has kindly provided a summary for each of the recent publications included below. If your site has a junior investigator or fellow interested in providing a short editorial for the next quarterly newsletter, please reach out to fagcc-info@curefa.org.

Lynch, David R et al. "Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data." Annals of clinical and translational neurology vol. 11,1 (2024): 4-16. doi:10.1002/acn3.51897 - Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data - PMC (nih.gov)

This study presents a post hoc analysis of the MOXIe extension phase, which supported the approval of omaveloxolone for the treatment of FA. The analysis compared MOXIe participants to matched FA patients recruited from the natural history study FACOMS. Over a 3-year observational period, changes from baseline in the neurological scale mFARS were significantly smaller in MOXIe extension participants than in FACOMS patients. These findings support a slower disease progression with omaveloxolone and emphasize the importance of natural history data in the drug approval process.

Rodden, Layne N et al. "Retinal hypoplasia and degeneration result in vision loss in Friedreich ataxia." Annals of clinical and translational neurology vol. 10,8 (2023): 1397-1406. doi:10.1002/acn3.51830 Retinal hypoplasia and degeneration result in vision loss in Friedreich ataxia - PMC (nih.gov)

This study examined retinal thickness and visual acuity in a large cohort of FA patients (n=198) compared to controls. The results showed that FA patients had pathologically thin retinas early in the disease, even at presentation, despite having intact high-contrast vision. Retinal thickness in FA worsened over the course of the disease and correlated with several established measures of disease severity. These findings suggest that visual system pathology in FA results from a combination of hypoplasia and superimposed degeneration.

Lynch, David R et al. "Frataxin analysis using triple quadrupole mass spectrometry: application to a large heterogeneous clinical cohort." Journal of neurology, 10.1007/s00415-023-12118-x. 8 Dec. 2023, doi:10.1007/s00415-023-12118-x Frataxin analysis using triple quadrupole mass spectrometry: application to a large heterogeneous clinical cohort | Journal of Neurology (springer.com)

In this study, the authors used a triple quadrupole mass spectrometry-based assay to measure the levels of two frataxin isoforms: FXN-M, found in most cells, and FXN-E, found almost exclusively in red blood cells. The study included 106 patients with FA. The FXN levels measured with this assay were found to be correlated with the neurological outcomes. The measurements obtained were more consistent than those obtained using previously applied whole blood assays. These findings demonstrate the potential of the assay as a biomarker for disease status.

Indelicato, Elisabetta et al. "Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study." Movement disorders: official journal of the Movement Disorder Society, 10.1002/mds.29687. 23 Dec. 2023, doi:10.1002/mds.29687 Predictors of Survival in Friedreich's Ataxia: A Prospective Cohort Study - Indelicato - Movement Disorders - Wiley Online Library

This paper reports the first prospective, multicenter survival analysis in FA based on data from the European FA Natural History Study. Three independent predictors of survival were identified: advanced neurological disability, history of cardiac arrhythmia, and diabetes mellitus. GAA repeat length and cardiac symptoms did not play a role in predicting survival. The authors created a score that predicts up to 10-year survival and may help identify patients who deserve closer follow-up and guide stratification for clinical trials.

Porcu, Luca et al. "Longitudinal changes of SARA scale in Friedreich ataxia: Strong influence of baseline score and age at onset." Annals of clinical and translational neurology vol. 10,11 (2023): 2000-2012. doi:10.1002/acn3.51886 Longitudinal changes of SARA scale in Friedreich ataxia: Strong influence of baseline score and age at onset - PMC (nih.gov)

This study investigated the dynamics of changes in the Scale for Assessment and Rating of Ataxia (SARA), a widely used outcome measure also in FA, using data from the European FA Natural History Study. In this cohort, SARA progression over 4 years of follow-up was mainly influenced by baseline score and age at assessment (the lower the baseline SARA score and age, the faster the progression). The SARA item assessing gait had the highest annual rate of progression.

Recent Publications (cont.)

Trantham, Shandra J et al. “Perspectives of the Friedreich ataxia community on gene therapy clinical trials.” Molecular therapy. Methods & clinical development vol. 32,1 101179. 18 Dec. 2023, doi:10.1016/j.omtm.2023.101179 Perspectives of the Friedreich ataxia community on gene therapy clinical trials - PMC (nih.gov)

This paper presents the results of a survey on the perception of the FA community regarding gene therapy trials. If given a choice between gene therapy targets, FA patients would prioritize the treatment of neurological issues over cardiac disease. Caregivers, on the other hand, are more likely to choose to treat cardiomyopathy. The survey responses highlight the urgency expressed by patients and caregivers in obtaining gene therapy, regardless of potential side effects.

Clayton, Russell et al. “Safety, pharmacokinetics, and pharmacodynamics of nomlabofusp (CTI-1601) in Friedreich's ataxia.” Annals of clinical and translational neurology, 10.1002/acn3.51971. 4 Feb. 2024, doi:10.1002/acn3.51971 Safety, pharmacokinetics, and pharmacodynamics of nomlabofusp (CTI-1601) in Friedreich's ataxia - Clayton - Annals of Clinical and Translational Neurology - Wiley Online Library

This paper presents the findings of a phase 1, double-blind, placebo-controlled study that evaluated the safety and tolerability of nomlabofusp, a fusion protein designed to deliver frataxin into mitochondria and increase intracellular frataxin levels. Nomlabofusp was administered subcutaneously at ascending doses and was generally well-tolerated. The treatment resulted in a significant, dose-dependent increase in tissue frataxin levels. This study is the first to investigate a frataxin replacement therapy in FA patients.

Di Pietro, G et al. “Nerve ultrasound in Friedreich's Ataxia: enlarged nerves as a biomarker of disease severity.” Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, vol. 159 75-80. 2 Feb. 2024, doi:10.1016/j.clinph.2024.01.004 Nerve ultrasound in Friedreich's Ataxia: enlarged nerves as a biomarker of disease severity - PubMed (nih.gov)

In this pilot study, high-resolution nerve ultrasound was used in addition to nerve conduction studies to evaluate peripheral neuropathy in 10 FA patients. The peripheral nerves in FA patients were found to be enlarged compared to controls, with a significant difference at multiple upper arm sites. The extent of peripheral nerve involvement, as evaluated by high-resolution ultrasound, correlated with several measures of disease severity.

Pilotto, Federica et al. “Omaveloxolone: a groundbreaking milestone as the first FDA-approved drug for Friedreich ataxia.” Trends in molecular medicine vol. 30,2 (2024): 117-125. doi:10.1016/j.molmed.2023.12.002 Omaveloxolone: a groundbreaking milestone as the first FDA-approved drug for Friedreich ataxia: Trends in Molecular Medicine (cell.com)

This paper reviews preclinical and clinical studies that led to the investigation of the NRF2 pathway as a therapeutic target and the approval of its activator, omaveloxolone, as the first FA treatment. The authors summarize preclinical evidence supporting the involvement of NRF2 and ferroptosis in FA pathology. They also discuss the contribution of natural history studies data in trial design and in the recent approval of omaveloxolone.

Indelicato E, et al. “Skeletal muscle proteome analysis underpins multifaceted mitochondrial dysfunction in Friedreich's ataxia.” Front Neurosci. 2023 Oct 31;17:1289027. doi: 10.3389/fnins.2023.1289027.
This study applied mass spectrometry-based proteome analysis to skeletal muscle biopsies of FA patients and controls. The analysis identified over 200 differentially expressed proteins in FA compared to controls, with approximately 75% being under the transcriptional control of NRF2, the target of the first approved FA drug, omaveloxolone. The present findings highlight the potential of skeletal muscle-omics as disease state readout in FA.

Grant/Funding Opportunities

FARA research grants

- Graduate Research fellowship – LOI deadline is March 15, 2024
- General Research Grants, Postdoctoral Fellowships and Research Awards – LOI deadline is August 15, 2024.

See FARA grant program priorities here:
https://www.curefa.org/grant-priorities
https://www.curefa.org/grant

Funding opportunities for rare disease research
FDA launched the FDA Rare Neurodegenerative Disease Grant Program https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/funding-opportunities-rare-disease-research

The agency awards grants and contracts to public and private entities to cover costs of research and development of interventions intended to prevent, diagnose, mitigate, treat or cure ALS and other rare neurodegenerative diseases in adults and children.

LifeArc funding opportunities
The LifeArc Philanthropic Fund provides grants and funding to academic researchers working to advance new treatments and diagnostics for rare diseases. https://www.lifearc.org/strategy/rare-disease-translational-challenge/rare-disease-research-funding/

ARPA-H funding opportunities
ARPA-H opened its first Agency-wide Open BAA, seeking funding proposals for research aiming to improve health outcomes across patient populations,
communities, diseases, and health conditions. The BAA calls for proposals to outline breakthrough research and technological advancements.
Opportunity to pursue novel ideas that are not currently covered by a program. Rolling submissions for 1 year. Revolutionary ideas required.
https://arpa-h.gov/engage/baa/

Grant opportunities from CIRM can be found at
www.cirm.ca.gov/researchers/funding-opportunities

Various MRC Funding Opportunities
https://www.ukri.org/opportunity/?filter_council%5B0%5D=824&filter_order=closing_date

Oxford-Harrington Rare Disease Centre Call for Proposals
The OHC's 2024 Rare Disease Scholar Award seeks novel approaches to treat rare diseases, with a focus on neurological disorders, developmental and metabolic disorders, and rare cancers. Researchers in the U.S., U.K., and Canada are eligible to apply for this award. The deadline to submit a full application is March 26, 2024
https://www.harringtondiscovery.org/news-media/2024/02/06/oxford-harrington-rare-disease-centre-opens-call-for-proposals

Upcoming Meetings

March 26
FA GCC Quarterly Meeting
8am ET | 1pm CET

June 25
FA GCC Quarterly Meeting
8am ET | 2pm CET

September 24
FA GCC Quarterly Meeting
8am ET | 2pm CET

November 12
2024 in-person meeting
at ICAR London
11am –1pm GMT

International Congress for Ataxia Research