

The Ataxia Global Initiative (AGI) SARA qualification program

Thomas Klockgether

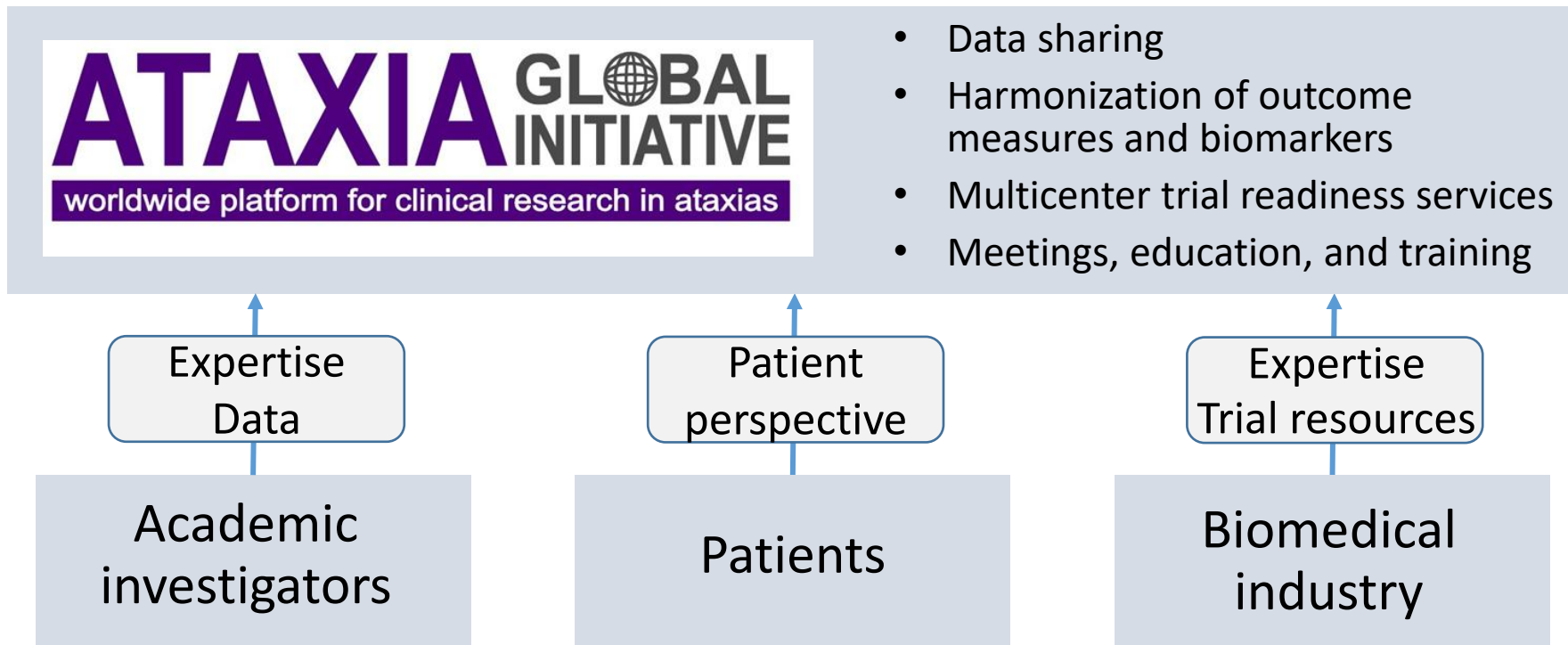
EuroAtaxia Patient Conference, Amsterdam (NL)
28 Oct 2025



Ataxia Global Initiative (AGI)

- The Ataxia Global Initiative (AGI) is a worldwide research platform that has the goal to facilitate the clinical development of therapies for ataxias.
- AGI has worldwide representation including Africa, East Asia, Australia, and Latin America with more than 400 members.
- AGI integrates all stakeholders in the ataxia field including 18 patient organizations.

Ataxia Global Initiative (AGI)



Harmonization of outcome measures and biomarkers

#1 Clinical outcome assessments & registries

WG leads: *Thomas Klockgether and Matthis Synofzik*

#2 Molecular biomarkers & biosampling

WG leads: *Liana Rosenthal, Giulia Coarelli, and Andrea Cortese*

#3 MRI biomarkers

WG leads: *Jennifer Faber and Pierre-Giles Henry*

#4 Digital-motor biomarkers

WG leads: *Andreas Träschütz and Adam Vogel*

#5 Model systems & preclinical trials

WG leads: *Magda Santana, Ronald Buijsen, Jeannette Hübener-Schmid, and Thorsten Schmidt*

#6 Next-generation genomics & platforms

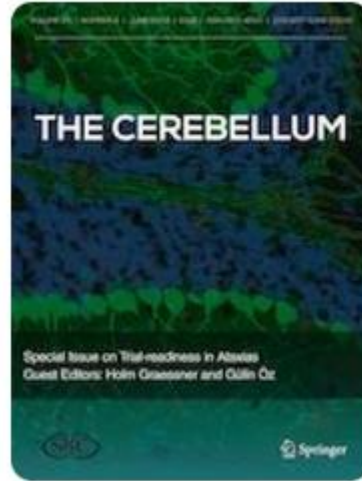
WG leads: *Brent Fogel, Andrea Nemeth, Matthis Synofzik and Stephan Zuchner*

#7 Policy and patient organization engagement

WG leads: *Julie Greenfield and Holm Graessner*

#8 Patient-reported experience & outcome measures

WG leads: *Tanja Schmitz-Hübsch and Bart-Jan Schuman*



Volume 23, Issue 3

June 2024

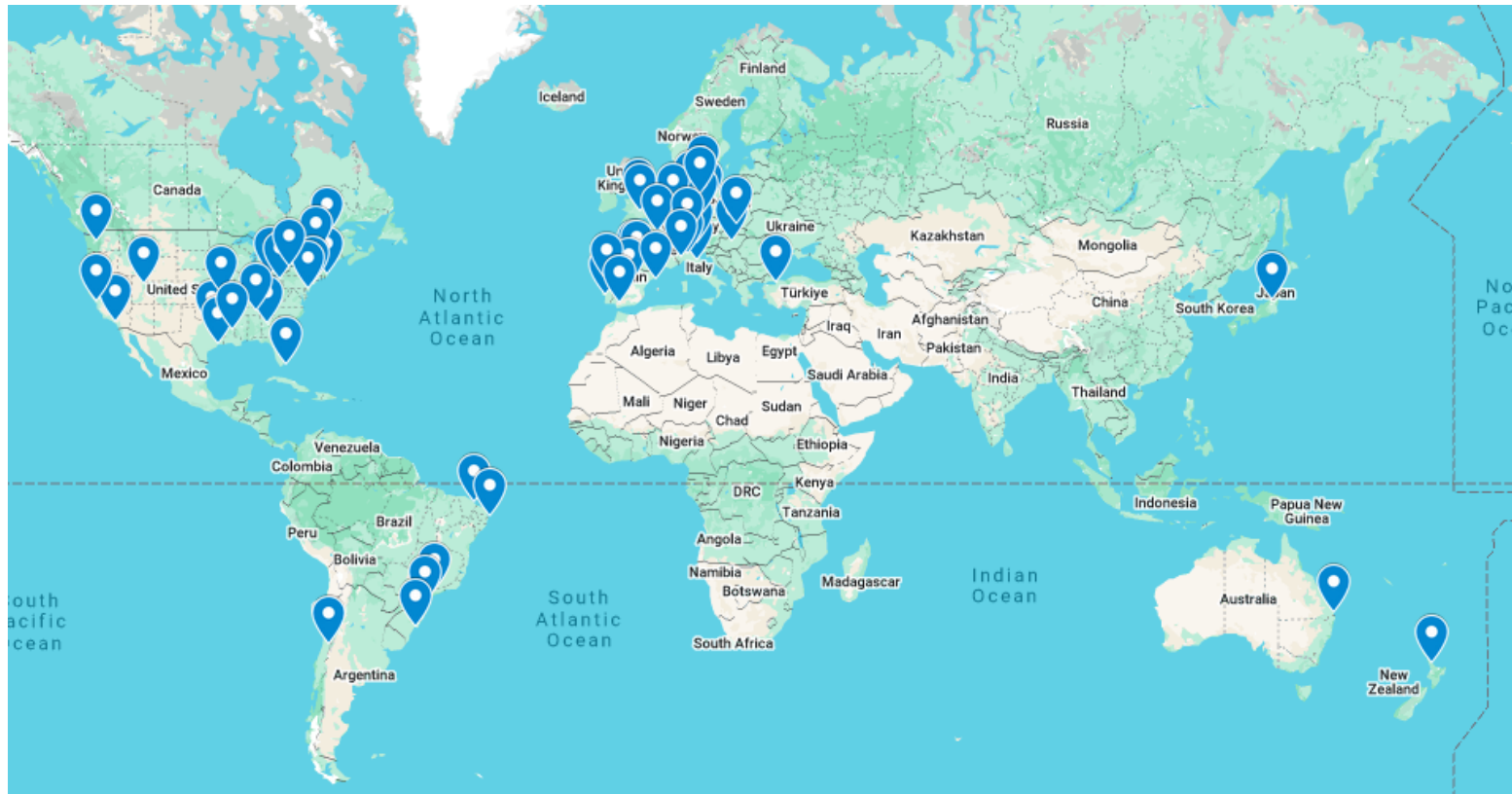
Special Issue on Trial-readiness in Ataxias

Issue Editors:

Holm Graessner, | Gulin Oz

Multicenter trial readiness services

The Trial Site Registry (TSR) is an online database of specialized sites that see patients with ataxias. It holds site-level information relevant to clinical studies, including trial experience, information on personnel, facilities, and ataxia patient populations in a readily available, standardized fashion.



Global TSR map

PREVENTIVE TRIALS FOR SCAS

ATAXIA GLOBAL
INITIATIVE
worldwide platform for clinical research in ataxias

AGI Expert Masterclass, 2026

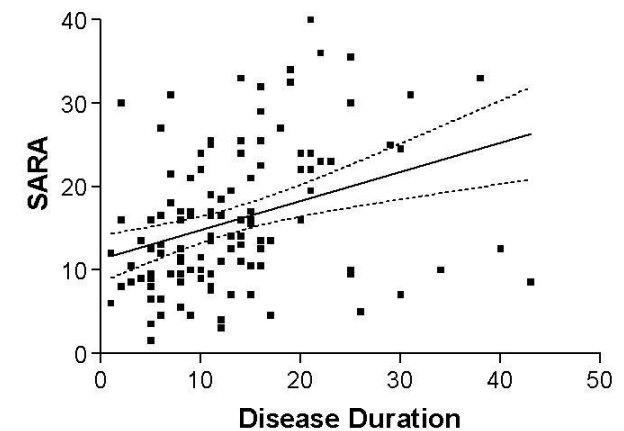
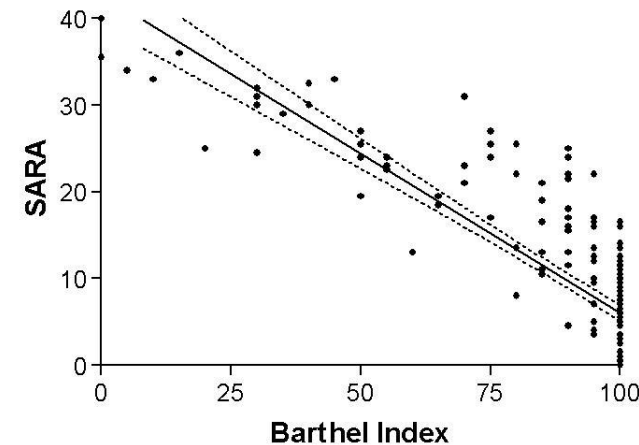
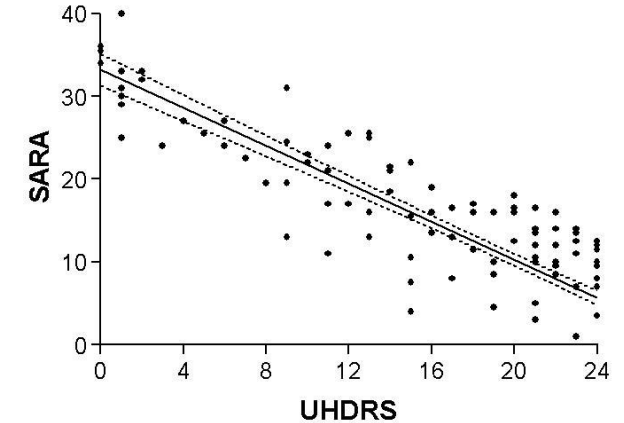
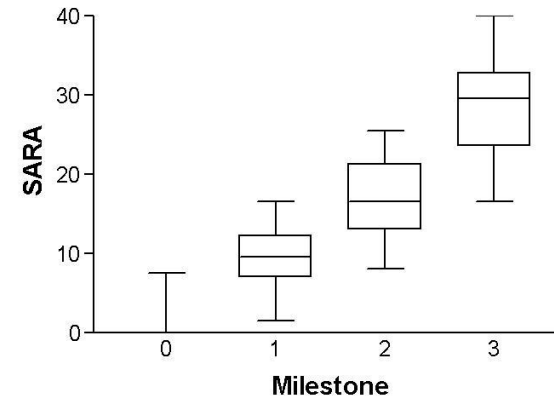
ATAXIA GLOBAL
INITIATIVE
worldwide platform for clinical research in ataxias

| First AGI Expert Masterclass, 2026

Genetics, Disease Mechanisms, and Trial Readiness in SCAs

Scale for the Assessment and Rating of Ataxia (SARA)

- **The Scale for the Rating and Assessment of Ataxia (SARA)** is a **clinician-reported outcome (ClinRO)** based on a standard neurological examination. SARA has 8 items.
- Various **validation trials** in ataxia patients (SCA, FRDA, ARSACS, sporadic ataxia) provided **evidence for validity, reliability, linearity, and sensitivity to change.**



Criticism of SARA

- SARA is widely used in observational and interventional trials, but there are unsolved issues regarding meaningfulness, metric properties, and application.
- In a number of instances, FDA did not accept SARA as the primary outcome.
- Modified and shortened versions of SARA have been used in ataxia trials.

SARA Qualification Program

The goal of the program is to **increase the acceptance and applicability of SARA** by

- establishing its **content validity and patient relevance** (qualitative approach),
- performing an **in-depth analyses of existing SARA data** (data-driven, quantitative approach), and
- preparing a **detailed SARA user manual** (expert consensus), and
- achieving **regulatory acceptance** (EMA).

Content validity and patient relevance

SARA has been developed based on physicians' concept of ataxia. There is the need to match this concept with patient perspective.

Approach

- Collect and analyze available data from patient interviews/questionnaires
- Create a list of symptoms ordered by frequency and importance for patients
- Map symptoms on SARA items



M. Grobe-Einsler

In depth-analysis of existing SARA data

General principles

- Disease-specific analysis: initial focus on SCA3 (EUROSCA, ESMI, READISCA, CRC-SCA) followed by other common SCAs and MSA-C
- Detailed analysis of performance of total score and of each item
- Stage-specific analysis (stage 1: disease onset, as defined by onset of gait difficulties; stage 2: loss of independent gait, as defined by permanent use of a walking aid or reliance on a supporting arm; stage 3: confinement to wheelchair, as defined by permanent use of a wheelchair (Klockgether et al. Brain 1998))

Planned analyses

- Sensitivity to change
- Clinical meaningfulness of change



T. Schaprian

In depth-analysis of existing SARA data

- **EUROSCA:** Enrolment of EUROSCA is completed. The cohort includes 122 SCA3 ataxic mutation carriers with at least one follow-up.
- **RISCA:** Enrolment of RISCA is completed. The cohort includes 26 SCA3 pre-ataxic mutation carriers with at least one follow-up.
- **READISCA:** Enrolment of READISCA is completed. The cohort includes 98 SCA3 pre-ataxic and early-ataxic mutation carriers with at least one follow-up.
- **ESMI:** ESMI is an ongoing study. By March 2025, ESMI included approximately 300 pre-ataxic and ataxic SCA3 mutation carriers with at least one follow-up.
- **CRC-SCA:** CRC-SCA is an ongoing study.

SARA user manual

- Preparation of a detailed SARA user manual based on expert consensus
- Rules for mapping of item 1, 2, and 4 on items with five response categories
- Adaptation of SARA training tool

EMA Qualification

Time plan

- Until end of 2025 – prediscussion meeting with EMA
- Until end of March 2026 – agreement on question(s) to be asked to EMA
- Until end of September 2026 – preparation of dossier including data package
- Start of EMA process – October 2026

Factors that might potentially influence timeline

- Outcome of prediscussion meeting
- Availability of required data package
- Fee to be paid to EMA and waiver thereof

H. Graessner



Governance

The **SARA Qualification Program** is a project of **Working Group #1** (Clinical outcome assessments & registries) of the **Ataxia Global Initiative (AGI)**.

Steering committee

T. Klockgether, H. Graessner, M. Grobe-Einsler, M. Potashman, T. Schmitz-Hübsch, C. Suart, M. Synofzik, S. Tezenas

Expert group

SARA authors, AGI members, ERN-RD members, industry representatives, patient representatives

Project status

- **Critical review and guidance** of the studies performed in the framework of the program
- Expert consensus on the **SARA user manual**

Time plan

| | |
|------------------|---|
| Aug 2025 | Expert Group kick-off meeting |
| Aug - Oct 2025 | Survey of SARA application (Expert Group) |
| Nov – Jan 2025 | Analysis of survey (M. Grobe-Einsler, T. Klockgether) |
| Feb 2026 | Consensus meeting on SARA application |
| March – May 2026 | Preparation of SARA user manual |
| June 2026 | Consensus meeting on SARA user manual |