AGI formats

https://ataxia-global-initiative.net

- working groups
- projects
- ressources
- Young Investigator Initiative

M. **Clinical outcomes & registries** #1 **Molecular biomarkers & biosampling** #2 E) #3 **MR** biomarkers 6 #4 **Digital-motor biomarkers** Model systems & preclinical trials **~** #5 ğ Next-generation genomics and platforms #6 #7 Policy and patient organization engagement

- tools & methods studios
- focus projects





AGI focus projects



- target the key bottlenecks in ataxia trial-readiness in particular: endpoints
- jointly prioritized and worked upon by academia, industry, CPTA and PAOs
- early interaction with **regulators**

Modification of SARA

Trial-ready analysis of NfL (incl anchoring in patient meaningfulness)

Trial-ready analysis of top digital-motor gait measures (incl anchoring in patient meaningfulness)

Capturing change in the the preataxic stage



AGI Focus Project

SARA modification

Matthis Synofzik, on behalf of AGI

AGI Conference, Addison (TX, USA) 04 Nov 2022

Scale for the Assessment and Rating of Ataxia (SARA)

The Scale for the Rating and Assessment of Ataxia (SARA) is a clinical rating scale based on a standard neurological exam. SARA has 8 items (gait, stance, sitting, speech, finger-chase, nosefinger, fast alternating movements, heel-shin).

Five validation trials in 617 ataxia patients (SCA, FRDA, sporadic ataxia) providing evidence for

- reliability
- validity
- linearity
- sensitivity to change



Schmitz-Hübsch et al. Neurology 2006;66:1717-20

Shortcomings

- 1. Patient meaningfulness of SARA has not been systematically addressed
- 2. SARA metrics not straight-forward, e.g.
 - items differentially contribute to the SARA sum score and have different sensitivity to change
 - SARA items have a different scoring range
- 3. Practical problems with the application of SARA

4. we should avoid an ever-increasing number of SARAs (SARA, fSARA, mSARA,.....)

potential shortcomings: different contributions and dynamics of the items



- Items differentially contribute to the SARA sum score and have different sensitivity to change.
- ... but also means:
- different information value in an IRT model of the SARA score
- avoids co-linearity

Traschütz et al. 2022, medRvix/under review

potential shortcomings

 Some items, such item 2 (stance), involve different tasks. 	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are
	open. For each condition, three trials are allowed. Best
	trial is rated.
	0 Normal, able to stand in tandem for > 10 s
	1 Able to stand with feet together without sway, but
	not in tandem for > 10s
	2 Able to stand with feet together for > 10 s, but only
	with sway
	3 Able to stand for > 10 s without support in natural
	position, but not with feet together
	4 Able to stand for >10 s in natural position only with
	intermittent support
	5 Able to stand >10 s in natural position only with
	constant support of one arm
	6 Unable to stand for >10 s even with constant support
	of one arm

shortcomings

SARA items 5 to 8:

- might measure the same clinical sign: dysmetria (FDA) •
- do not directly assess the ability to function in daily life (FDA; Maas et al, 2021 PRD) •

5) Finger chase

6) Nose-finger test

Rated separately for each side

Rated separately for each side Proband sits comfortably. If necessary, support of feet Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger movements in unpredictable directions in a frontal plane, which is in front of the proband at about 90 % of at about 50 % of proband's reach. Movements have an proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

and performs 5 consecutive sudden and fast pointing

- 0 No dysmetria
- 1 Dysmetria, under/ overshooting target <5 cm
- 2 Dysmetria, under/ overshooting target < 15 cm
- 3 Dysmetria, under/ overshooting target > 15 cm 4 Unable to perform 5 pointing movements

Tremor with an amplitude < 2 cm

0 No tremor

- 2 Tremor with an amplitude < 5 cm
- 3 Tremor with an amplitude > 5 cm
- 4 Unable to perform 5 pointing movements

Score	R ight	Left	Score	R ight	Left
mean of both sides (R+L)/2			mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of to the opposite knee, slide down along the shin to the the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- 0 Normal, no irregularities (performs <10s)
- 1 Slightly irregular (performs <10s) 2 Clearly irregular, single movements difficult
- to distinguish or relevant interruptions, but performs <10s 3 Very irregular, single movements difficult
- to distinguish or relevant interruptions, performs >10s 4 Unable to complete 10 cycles

8) Heel-shin slide

Rated separately for each side

Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

0 Normal 1 Slightly abnormal, contact to shin maintained

- 2 Clearly abnormal, goes off shin up to 3 times during 3 cycles
- 3 Severely abnormal, goes off shin 4 or more times during 3 cycles
- 4 Unable to perform the task

- Score Right Left Right Left Score mean of both sides (R+L)/2 mean of both sides (R+L) / 2

SARA modification

Objective

Develop SARA into a generally accepted clinician-reported outcome (ClinRO) that can be used in upcoming clinical trials

joint work by: academia, industry, statisticians, CPTA, + early interaction with regulators

• 1st Consensus conference (24+25th Jan 2023)

- Should SARA cover the entire range of severity or focus on specific stages?
- Which are the criteria for patient relevance and clinical meaningfulness?
- Which are the major shortcomings in metrics and practical application?

• Data analysis (Feb – July 2023)

- Develop an analytical plan based on outcome of consensus conference
- Form working groups and perform analysis
- 2nd consensus conference (Aug 2023) Consolidate results and agree on modified version
- Validation study

AGI formats

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- AGI perspectives/white papers

#1	Clinical outcomes & registries	₩₩.
#2	Molecular biomarkers & biosampling	
#3	MR biomarkers	E
#4	Digital-motor biomarkers	W
#5	Model systems & preclinical trials	(r [
#6	Next-generation genomics and platforms	X
#7	Policy and patient organization engagement	







AGI position perspective

Principles to guide data and sample sharing from treatment trials in degenerative ataxias

Matthis Synofzik, on behalf of AGI

AGI Conference, Addison (TX, USA) 04 Nov 2022



Principles to guide data and sample sharing from treatment trials in degenerative ataxia

the problem/need

- 1. data from treatment trials are of high importance for improving trial designs & analysis of upcoming trials
 → even if not effective and in particular from the placebo group
- 2. ethical responsibility to trial participants (particpate even for placebo!) to use and share these data
 - allow to learn & use these data (even if not effective, and from placebo treatment)
 - should be made accessible to the ataxia field (academia, pharma, PAOs)

trial sponsors (pharma, academia) should:

- 1. adhere to ataxia trial data sharing guidelines
 - to be articulated by AGI (cf. CAP guidelines, Weninger et al, 2016, for AD)

example from Alzheimer's field



Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials

Stacie Weninger^{a,*}, Maria C. Carrillo^{b,**}, Billy Dunn^c, Paul S. Aisen^d, Randall J. Bateman^e, Joanne D. Kotz^a, Jessica B. Langbaum^f, Susan L. Mills^e, Eric M. Reiman^f, Reisa Sperling^g, Anna M. Santacruz^e, Pierre N. Tariot^f, Kathleen A. Welsh-Bohmer^h

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^aDepartment of Neurology, Mashington University, St Louis, MO, USA
^bDepartment of Neurology, Brigham and Women's Hospital, Boston, MA, USA
^bDepartments of Neurology, & Psychiatry, Duke Dimer's ID, Southern NC, USA

Facilitating data sharing

- Where possible, standardized data acquisition techniques and assessments should be included to enhance the ability to compare data between trials.
- Measurement of multiple potential biomarkers should be included in trial designs to facilitate the identification of biomarkers of disease evolution and treatment response that could be used in future trials.

Sharing prerandomization data

• Screening and prerandomization baseline data should be made available to the scientific community within 12 months of enrollment completion.

Sharing postrandomization data before trial completion

• Emerging data from ongoing trials should be made available as soon as possible without compromising trial integrity, as progress in the field will be accelerated greatly by timely access to interim results such as well-characterized longitudinal fluid and imaging Sharing postrandomization data after trial completion

• All study data should be made available to the scientific community after the earlier of either regulatory approval of the tested treatment or 18 months after the completion or early termination of the trial.

Sharing biological samples

• The first priority for sample use is proper conduct of the study, which includes appropriate retention of samples in sufficient quantities for analyses during ongoing trials as well as for confirmatory testing after trial completion.





Principles to guide data and sample sharing from treatment trials in degenerative ataxia

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 - e.g. AGI Data Platform, RDCA-DAP

Ataxia Data Archive

example from Prevention Initative (FPI) - Minimal Data Sharing Platform

FPI MDS Platform: Data Explorer

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FPI FPI MDS Platform: Analysis Module







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- 2. share treatment trial data in a open accessible archive
 - e.g. AGI Data Platform, RDCA-DAP
- 3. ensure establishment and use of unique global GUID per patient
 - which permits data sharing and analysis across studies
 - mid- to long-term goal

unique global ID for each ataxia patient

to be used in all observational studies and clinical trials

- enable data sharing
- enable correction of NHS trajectories for participation in treatment trials



→ recommend all sponsors to include appropriate wording in consent forms to allow GUIDs to be created

EUPID – European Patient Identity Management



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- leverage learning from other fields (AD, MS, ALS) on how to improve data sharing from industry



ATAXIA GL@BAL

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