Clinical scales for ataxia: current state and ongoing developments

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11th July 2023

UNIVERSITÄT BONN

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DZNE

ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

Webinar outline

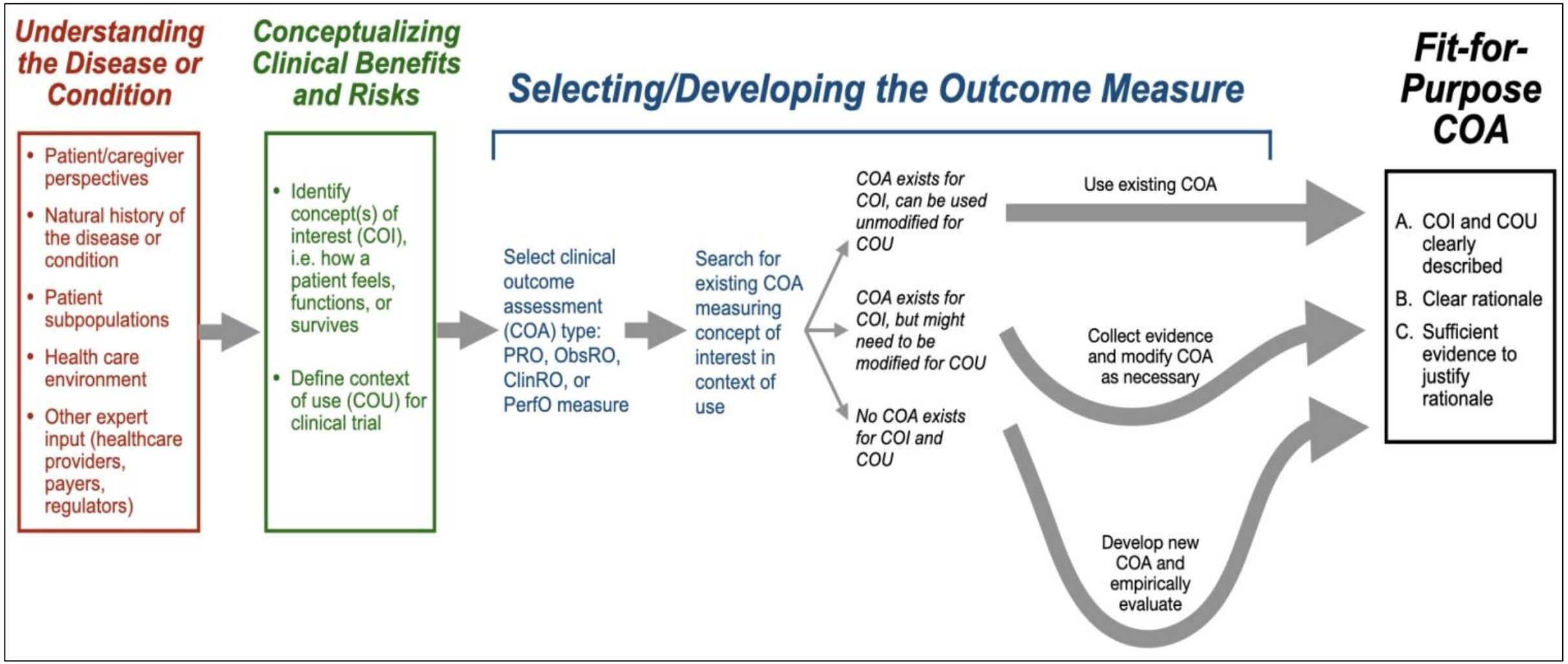
- Clinical outcome assessments (COAs)
- Clinician-reported outcomes (ClinROs) for ataxia
- Weaknesses of SARA and options for modification

Types of Clinical Outcome Assessments (COAs)

- **Patient-reported outcome** (PRO) measures (Appendix A)
  - Reports come directly from the patient
  - Useful for assessment of symptoms (e.g., pain intensity, shortness of breath), functioning, events, or other aspects of health from the patient's perspective
- **Observer-reported outcome** (ObsRO) measures (Appendix B)
  - Reports come from someone other than the patient or a health professional (e.g., a parent or caregiver) who has opportunity to observe the patient in everyday life
  - Useful when patients such as young children cannot reliably report for themselves, or to assess observable aspects related to patients' health (e.g., signs, events, or behaviors)
- **Clinician-reported outcome** (ClinRO) measures (Appendix C)
  - Reports come from a trained health-care professional using clinical judgment
  - Useful when reports of observable signs, behaviors, clinical events, or other manifestations related to a disease or condition benefit from clinical judgment
- **Performance outcome** (PerfO) measures (Appendix D)
  - A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions

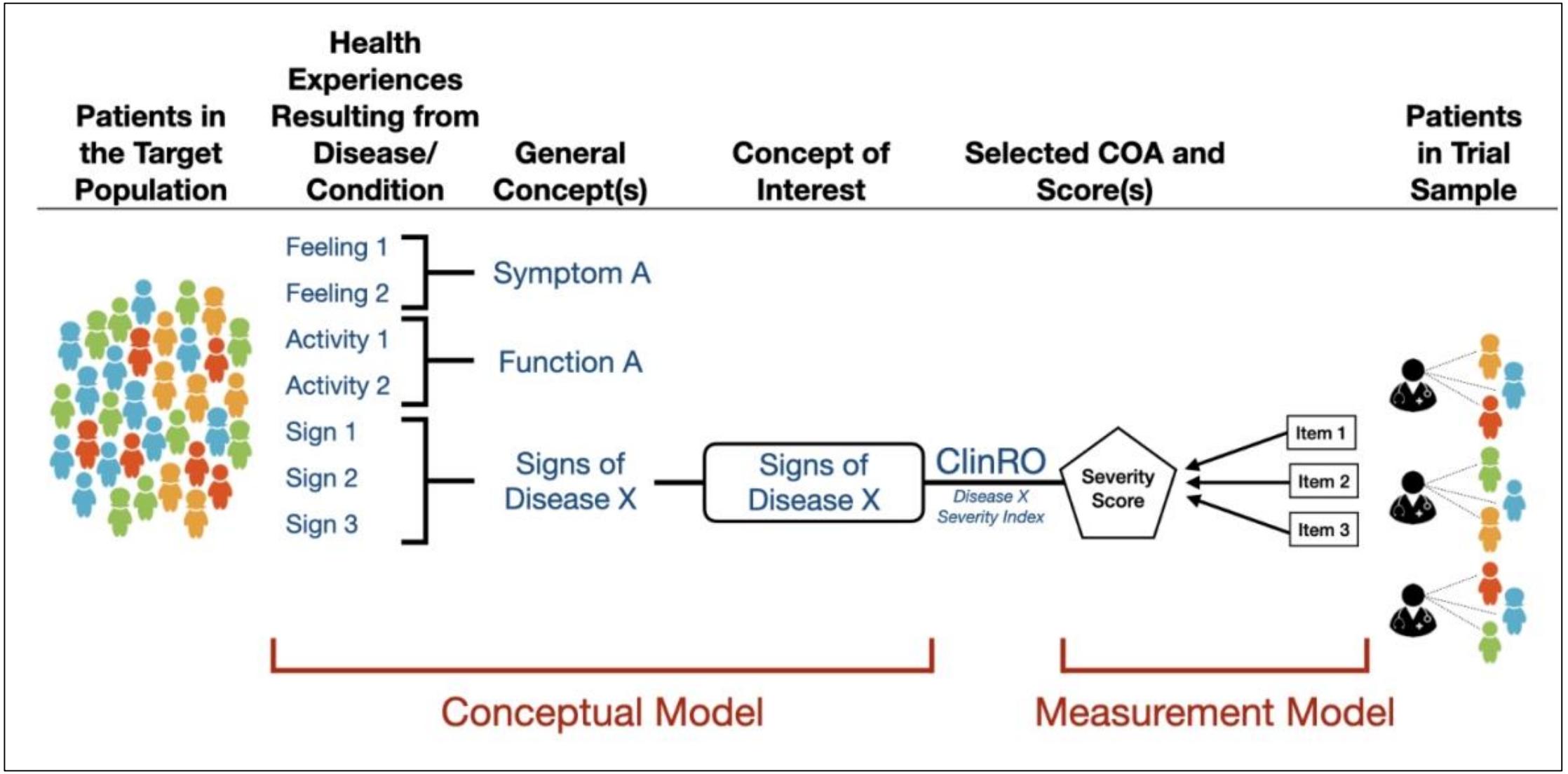
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

Patient-focused outcome measurement in clinical trials



https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

Conceptual framework for a Concept of Interest (COI)



https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

ClinROs for ataxia

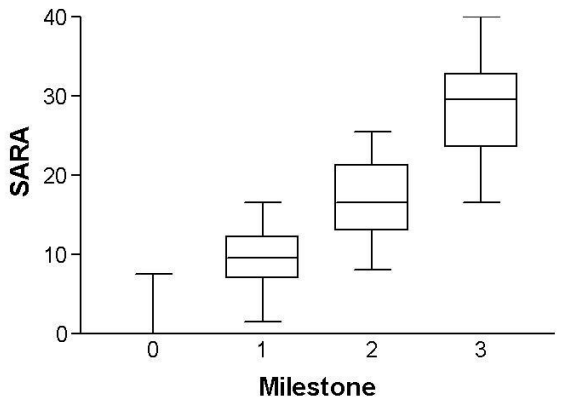
	Disease	Items	Weight (%)	Publication
ICARS	Ataxia	19	Posture/gait 34 Limb 52 Speech 8 Oculomotor 6	Trouillas et al. J Neurol Sci. 1997
FARS part III	FRDA	23	Posture/gait 24 Limb 39 Speech 8 Others 29	Subramony et al. Neurology 2005
SARA	SCA, FRDA, Sporadic ataxia	8	Posture/gait 45 Limb 40 Speech 15	Schmitz-Hübsch et al. Neurology 2006
NESSCA	SCA3	18	Posture/gait 10 Limb 8 Speech 10 Oculomotor 10 Others 62	Kieling et al. Eur J Neurol 2008
BARS	Ataxia	5	Posture/gait 27 Limb 53 Speech 13 Oculomotor 7	Schmahmann et al. Mov Disord. 2009

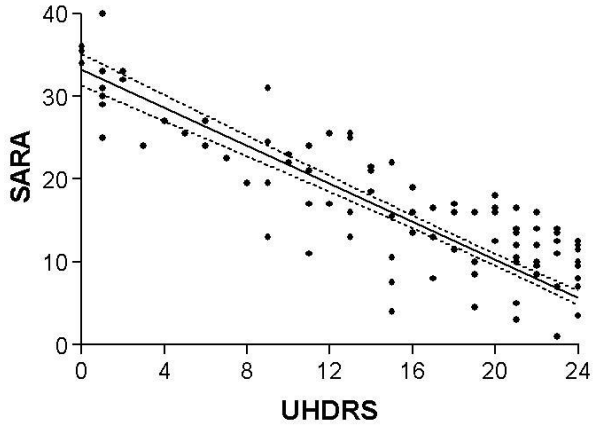
Scale for the Assessment and Rating of Ataxia (SARA)

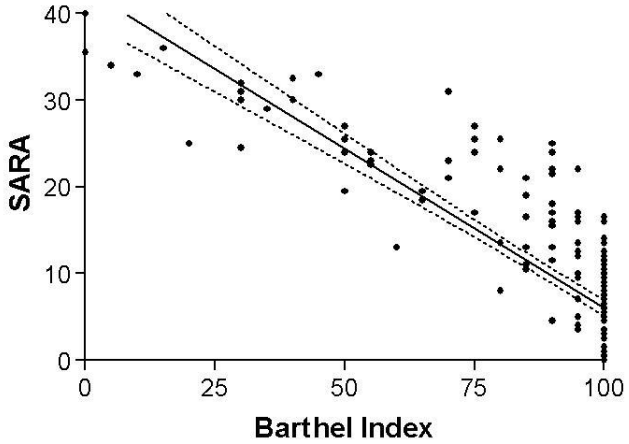
The Scale for the Rating and Assessment of Ataxia (SARA) is a clinical rating scale based on a standard neurological exam. SARA has 8 items (gait, stance, sitting, speech, finger-chase, nose-finger, fast alternating movements, heel-shin).

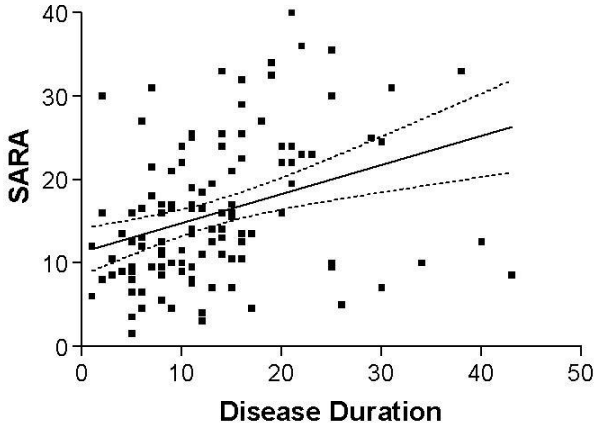
Five validation trials in 617 ataxia patients (SCA, FRDA, sporadic ataxia) providing evidence for

- reliability
- validity
- linearity
- sensitivity to change









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

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Download

http://www.ataxia-study-group.net/html/about/ataxiascales

SARA Online Training Tool

https://ataxia-global-initiative.net/resources/sara-training-tool/

SARA^{home}

Grobe-Einsler et al. Mov Disord 2021;36:1242-46

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

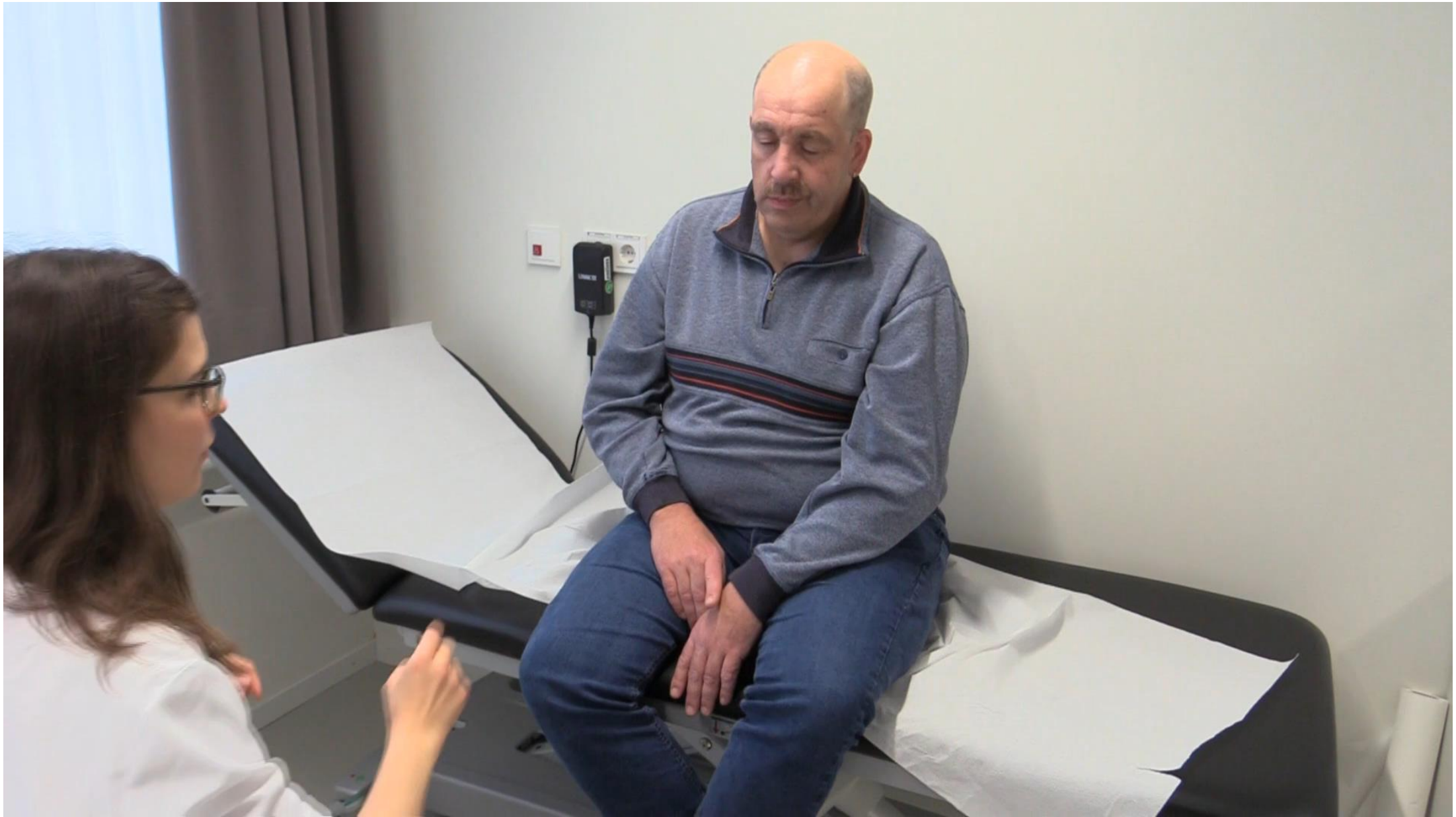
Item 1: Gait

Item 2: Stance

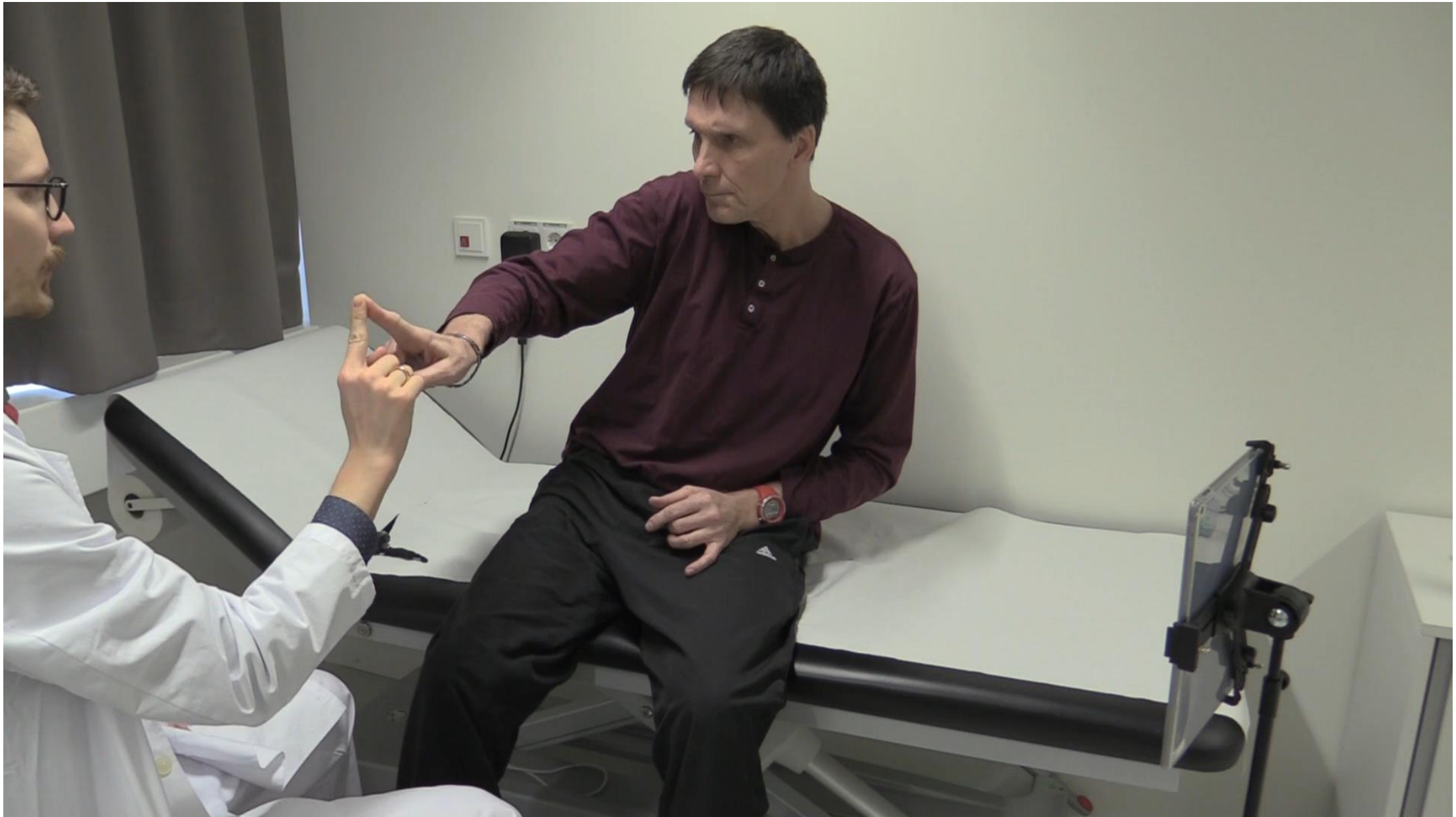
Item 3 - Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

Item 5: Finger-chase

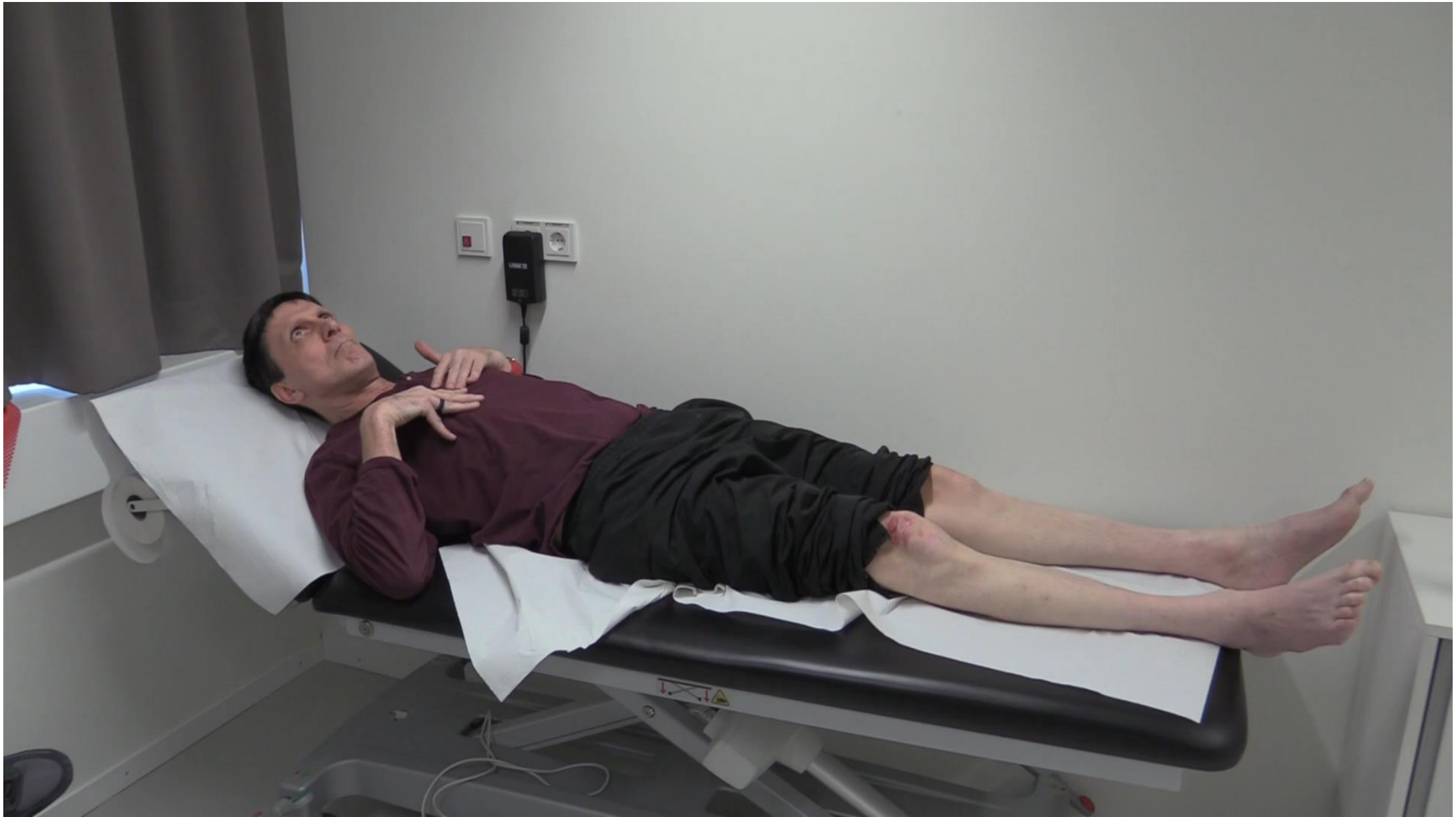


Item 6: Nose-finger

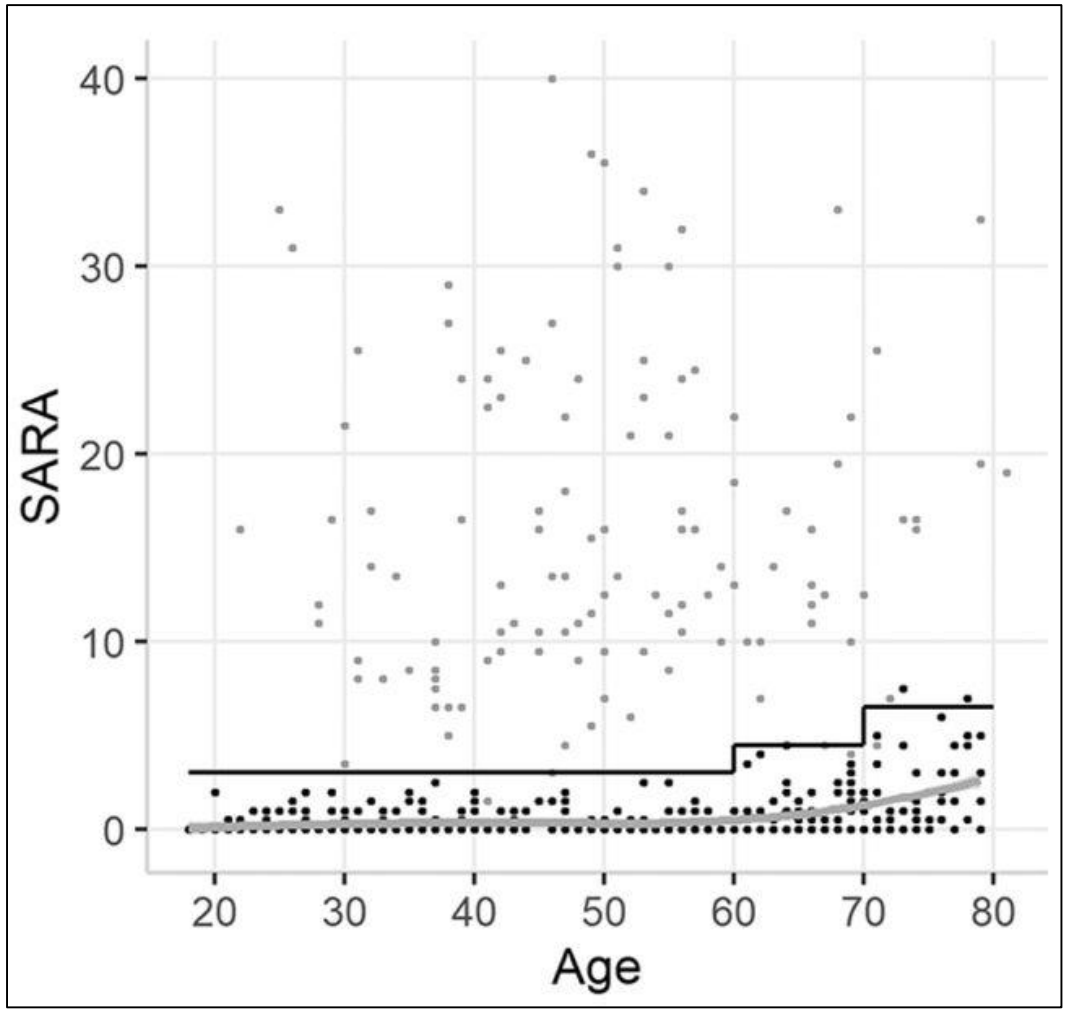


Item 7: Fast alternating movements

Item 8: Heel-shin



SARA in healthy individuals



SARA cut-off

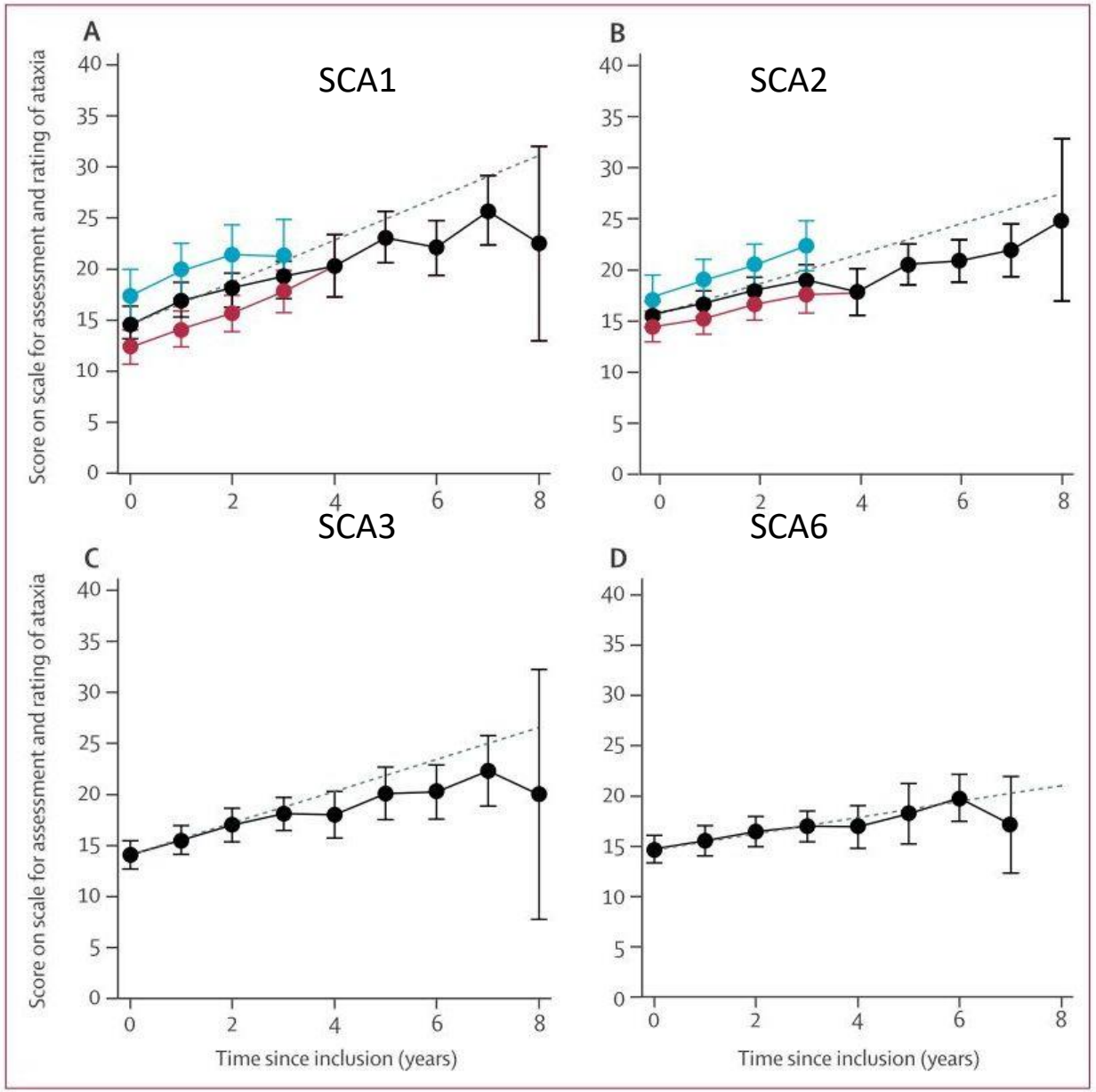
3.0 (20 – 60 years)

4.5 (60 – 70 years)

6.5 (> 70 years)

Grobe-Einsler et al. Eur J Neurol 2023;30:548-51

SARA progression in SCA patients



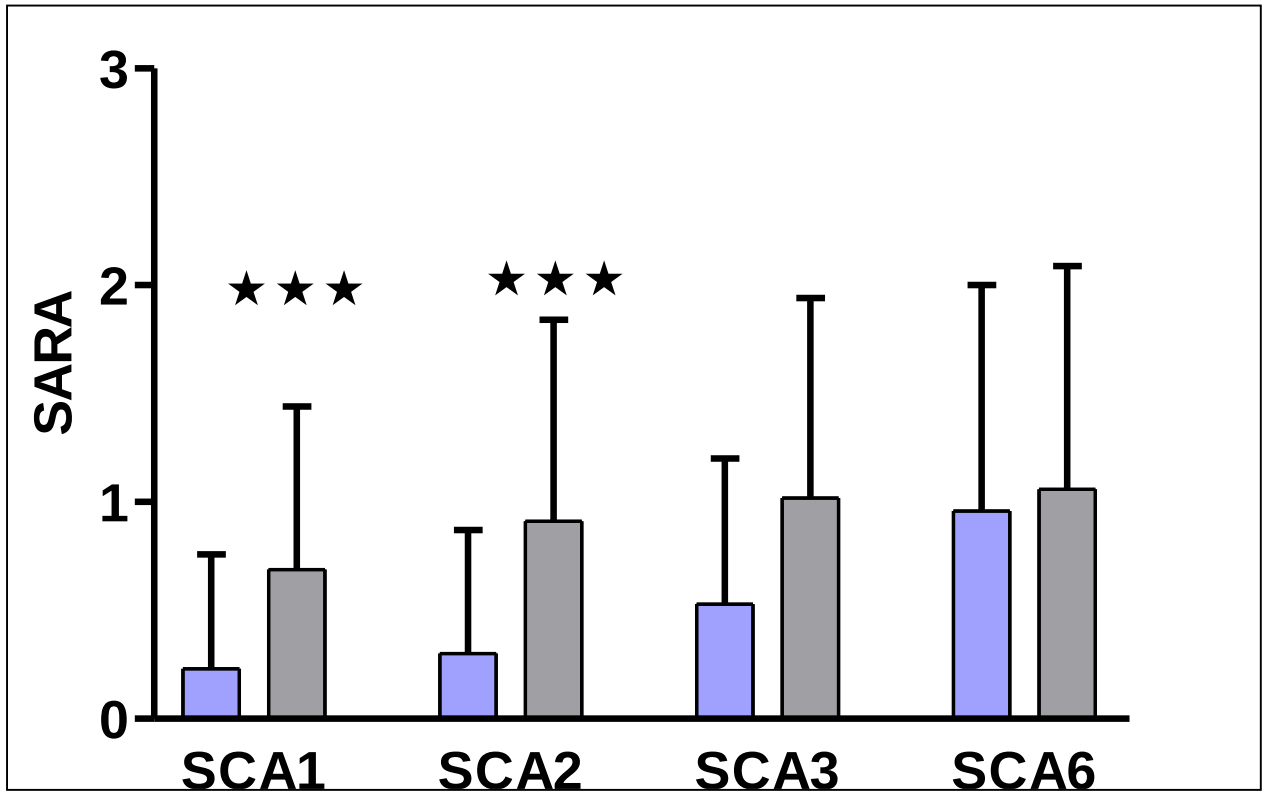
EUROSCA

Linear mixed and pattern mixture modelling

- SARA progression was linear in all genotypes.
- SARA progression was fastest in SCA1, intermediate in SCA2 and SCA3, slowest in SCA6.

Jacobi et al. Lancet Neurol 2015;14:1101-8

SARA in pre-ataxic SCA mutation carriers



RISCA

Multicentric prospective longitudinal observational cohort study

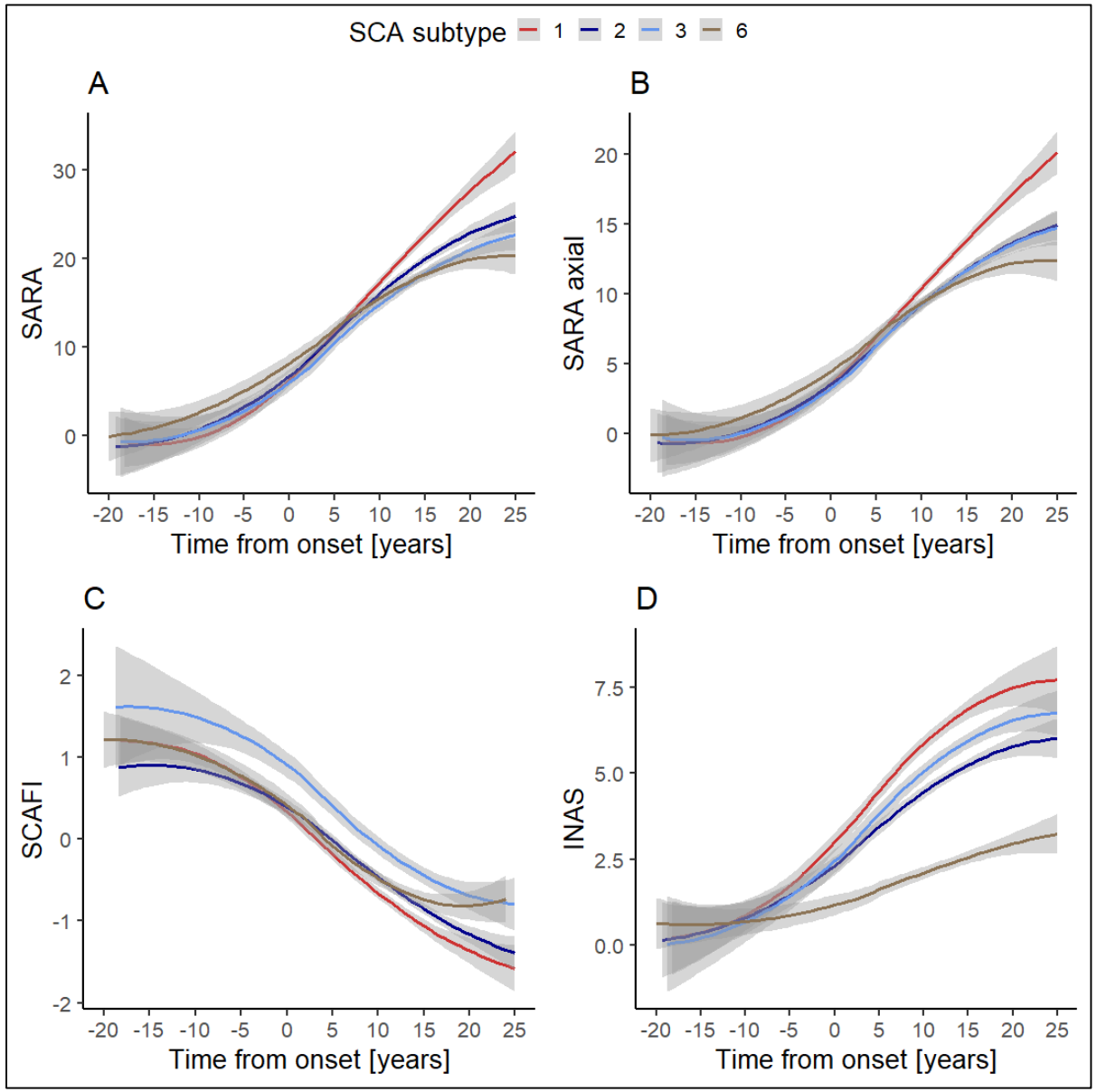
2008 – 2015

302 SCA1, SCA2, SCA3, or SCA6 risk persons

61 of 128 mutation carriers converted to manifest ataxia

Jacobi et al. Lancet Neurol 2013;12:650-8
Jacobi et al. Lancet Neurol 2020;19:738-47

SARA progression in SCA mutation carriers



Combined analysis of longitudinal data of clinical data of EUROSCA and RISCA cohort

677 mutation carriers

2740 visits

Jacobi et al. Ann Clin Transl Neurol 2023, positively reviewed

Functional SARA in Biohaven troriluzole trial

"The Biohaven clinical trials in SCA were a first of its kind in this area and utilized a newly developed rating scale (the functional SARA or f-SARA) that was developed in close consultation with the FDA using standard regulatory pathways to elucidate this new scale."

https://ir.biohaven.com/news-releases/news-release-details/biohaven-provides-overview-clinical-progress-regulatory-updates

SARA in N-acetyl-L-leucine trial in Niemann-Pick C

Fields *et al. Trials* (2023) 24:361
https://doi.org/10.1186/s13063-023-07399-6

Trials

STUDY PROTOCOL Open Access

N-acetyl-L-leucine for Niemann-Pick type C: a multinational double-blind randomized placebo-controlled crossover study

T Fields[1*], T M. Bremova[2], I Billington[1], GC Churchill[3], W Evans[4,5], C Fields[1], A Galione[3], R Kay[6], T Mathieson[4,6], K Martakis[7], M Patterson[8], F Platt[3], M Factor[1] and M Strupp[9]

SARA in N-acetyl-L-leucine trial in Niemann-Pick C

- Phase 3 trial met the primary endpoint and key secondary endpoints showing high statistical significance
- IB1001 (N-Acetyl-L-Leucine) showed a clinically meaningful improvement in symptoms, functioning, quality of life, and cognition in both pediatric and adult patients with NPC
- IB1001 was safe and well-tolerated with a favorable safety profile consistent with previous clinical and pre-clinical studies
- Based on these positive results, IntraBio plans to file for marketing authorization with IB1001 with the FDA and EMA

June 29, 2023, 8:00 AM EDT

The primary endpoint of the trial evaluated the impact of IB1001 on the Scale for the Assessment and Rating of Ataxia (SARA) compared to placebo after 12 weeks. Treatment with IB1001 demonstrated a statistically significant and clinically meaningful 1.37-point reduction of the SARA score compared to placebo (-1.97 on IB1001 vs. -0.60 on placebo; $p<0.001$).

https://intrabio.com/2023/06/29/intrabio-announces-positive-pivotal-trial-results-of-ib1001-for-the-treatment-of-niemann-pick-disease-type-c/

Friedreich Ataxia Rating Scale (FARS)

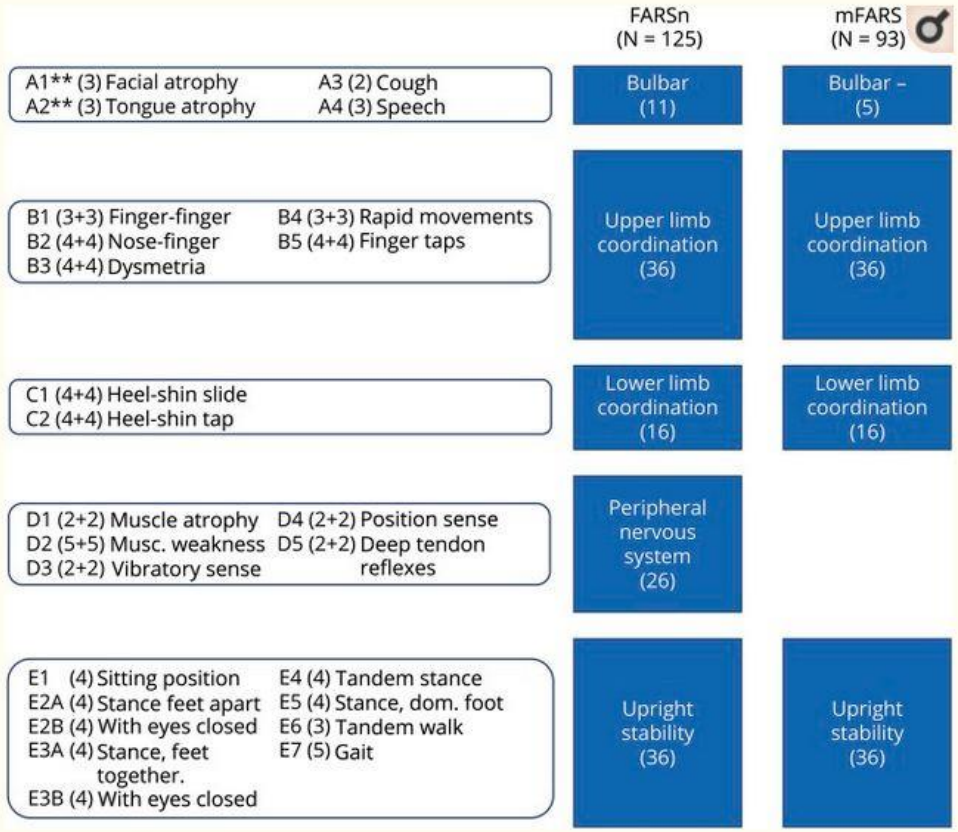


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Figure 1

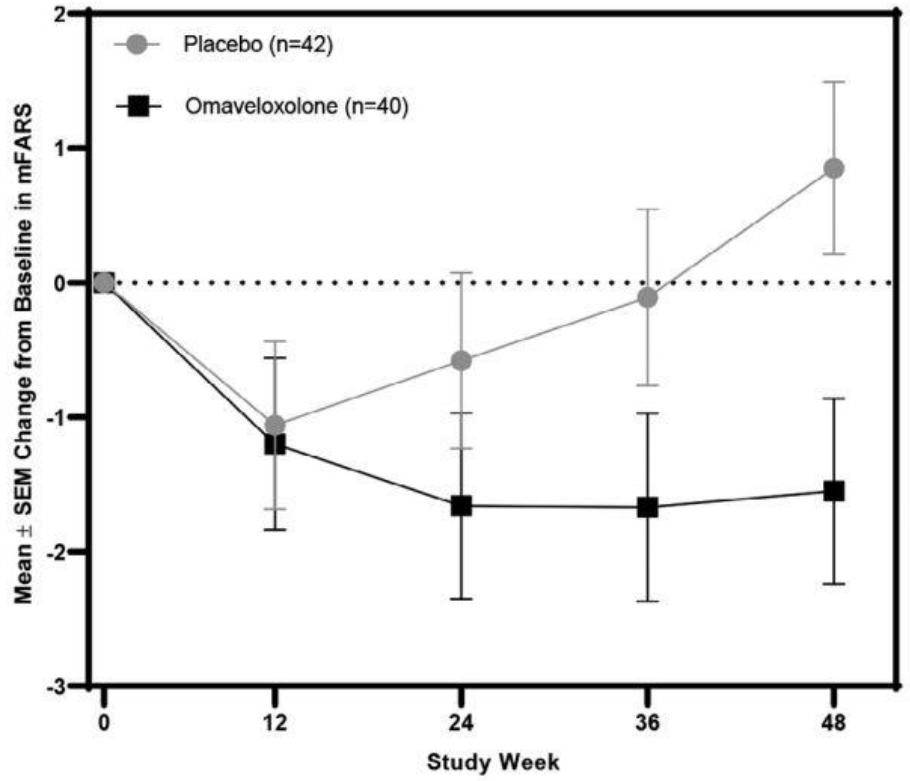
Measurement model of the neurologic examination of the FARSn and the modified FARS (mFARS)

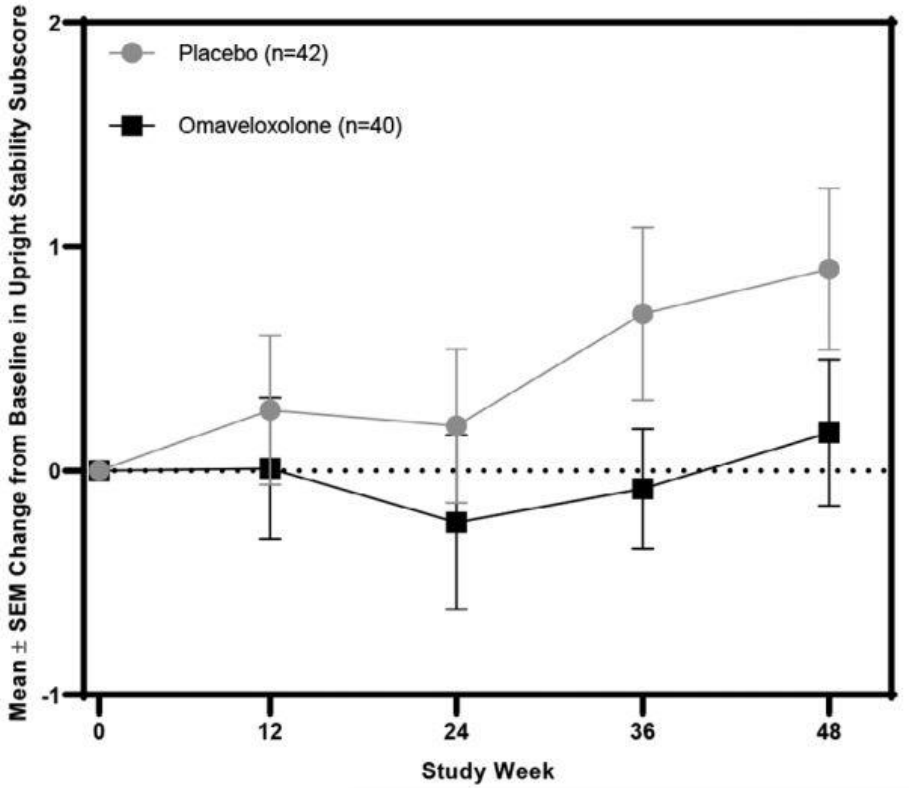
Maximum score/subscale/item scores are shown in brackets. Items in subscales B, C, and D are conducted separately on lateral sides; ** items A1 and A2 are excluded in the mFARS examination. FARS = Friedreich Ataxia Rating Scale; mFARS = modified FARS.

Rummey et al. Neurology Genet 2019;5:371

mFARS in MOXIe trial

- Nuclear factor erythroid 2-related factor 2 (Nrf2) is translocated to the nucleus in response to oxidative stress and induces expression of antioxidative genes.
- Nrf2 signaling is impaired in Friedreich´s ataxia.
- Omaveloxolone is a potent Nrf2 activator.





Lynch et al. Ann Neurol 2021; 89:212–25

Weaknesses of SARA: Meaningfulness

An endpoint based on a COA should

- reflect an aspect of the patient's health that is meaningful, and
- be capable of supporting an inference of treatment effect within the context of the planned clinical trial.

- Is ataxia a valid concept of interest?
- Are all SARA items meaningful?

- Analyse available data on symptoms experienced by ataxia patients and their impact on daily life
- Analyse relation of SARA total score and single items scores to patient experience

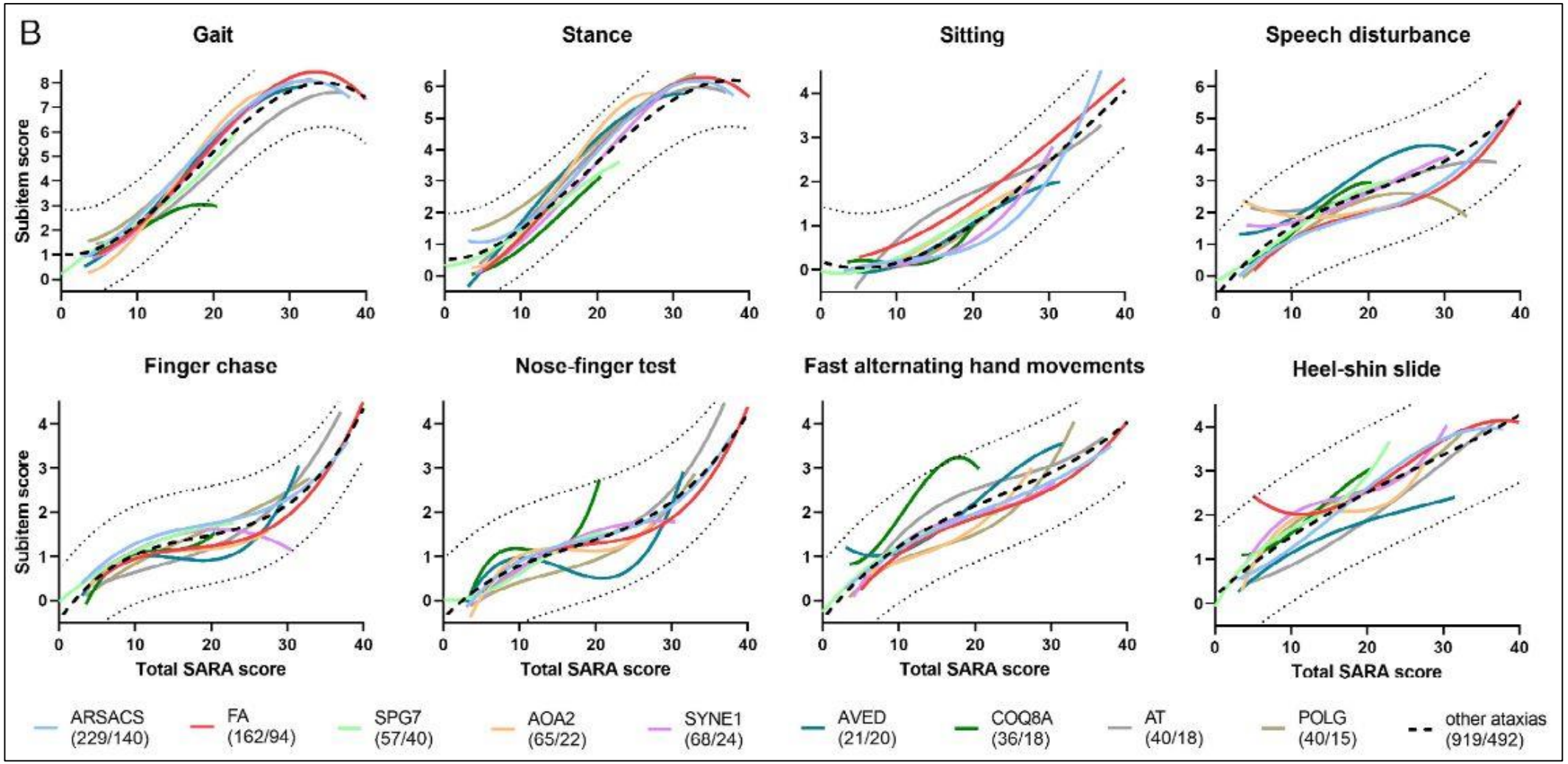
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

Weaknesses of SARA: Differential contribution of single items

	Annual change (n = 156)	
	Mean ± SD	**% of total**
Single items		
Gait	0.24 ± 0.87	15.8
Stance	0.27 ± 1.04	17.9
Sitting	0.27 ± 0.73	17.9
Speech	0.20 ± 0.72	13.2
Finger chase	0.11 ± 0.60	7.0
Nose-finger test	−0.02 ± 0.65	−1.1
Diadochokinesia	0.21 ± 0.76	14.1
Heel-shin slide	0.23 ± 0.76	15.1

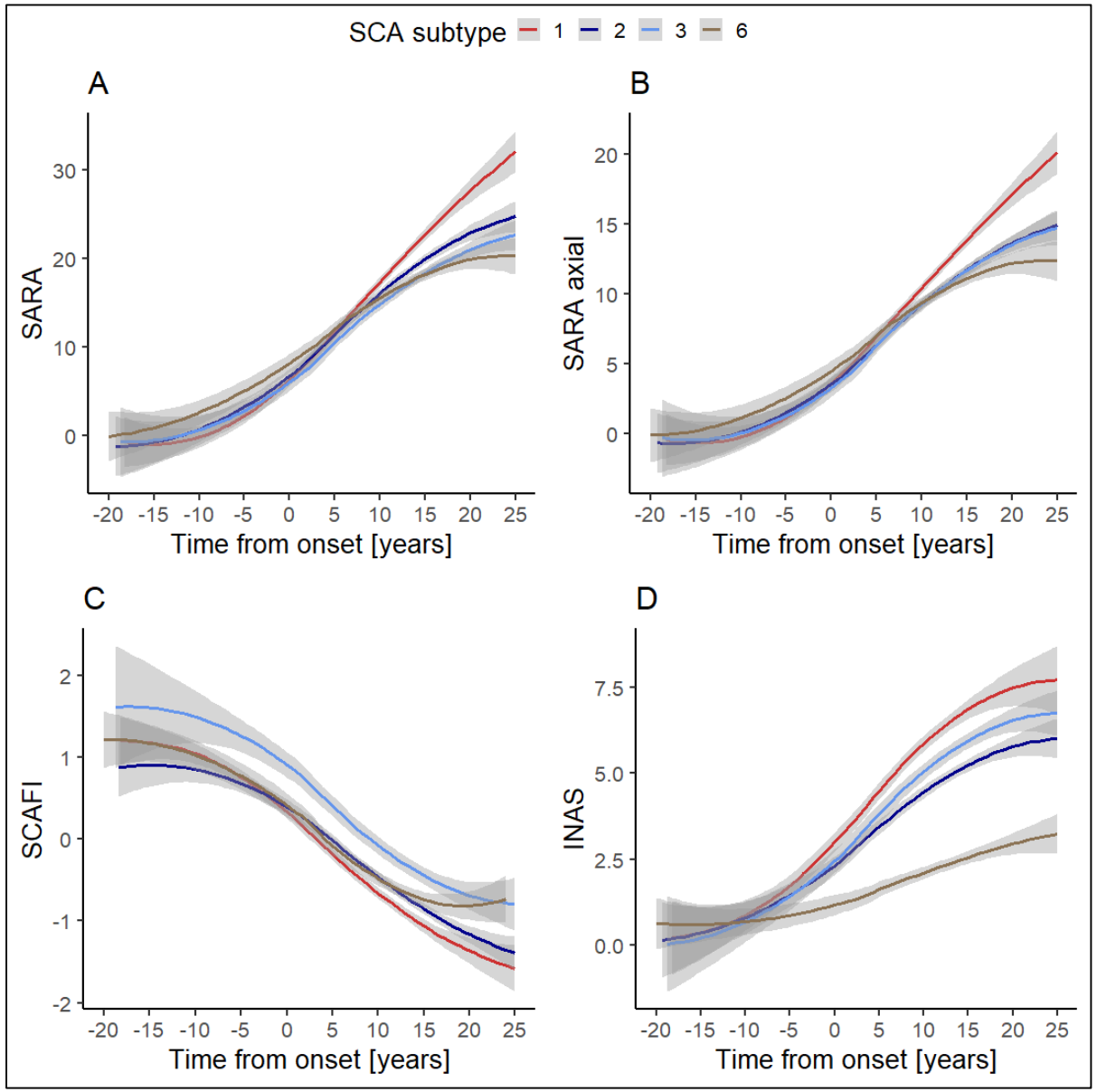
Maas et al. Mov Disord. 2022;37: 1850–60

Weaknesses of SARA: Differential contribution of single items



Traschütz et al. Ann Neurol 2023 doi: 10.1002/ana.26712

Weaknesses of SARA: Differential contribution of single items



Combined analysis of longitudinal data of clinical data of EUROSCA and RISCA cohort

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Weaknesses of SARA: Differential contribution of single items

COA	SCS [95% CI]
SARA	1.227 [1.224-1.230]
$SARA_{axial}$	0.920 [0.918-0.923]
SCAFI	-0.827 [0.830-0.824]
INAS	0.509 [0.507-0.512]

SCA3

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Weaknesses of SARA: Differential contribution of single items

Item Response Theory (IRT) is a type of latent variable models used for the analysis of a composite assessment data on the item level. It quantifies the relationship between the probability of a particular response to an assessment's item and an unobserved latent variable

- SARA captures one single latent variable.
- Analysis of the item characteristics shows that all items have good discrimination values.
- All items were informative with varying levels depending on the ataxia severity level.

Mats Karlsson, personal communication

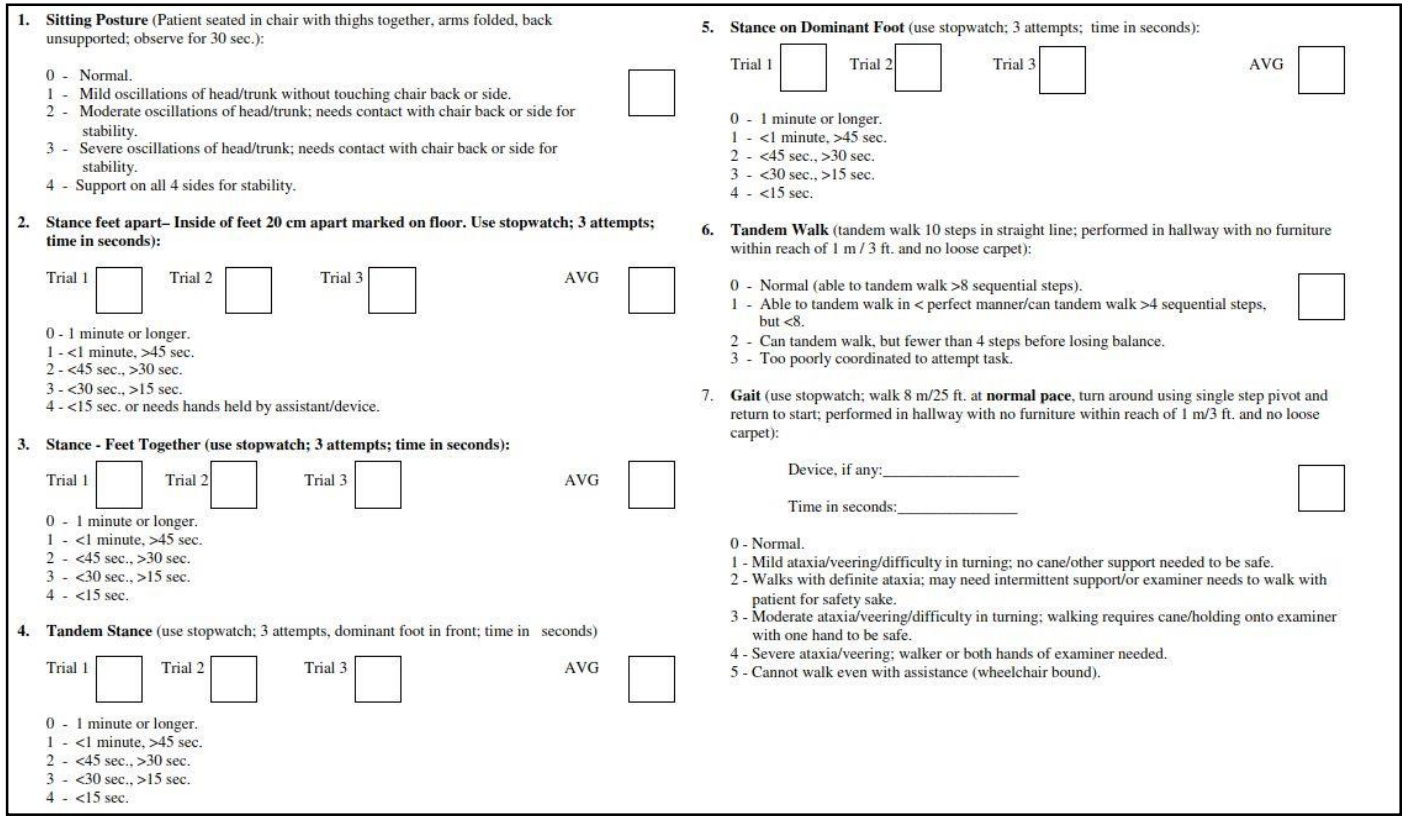
Develop optimized SARA

- Define concept of interest (COI)
- Analyse meaningfulness of single items and modify, if necessary
- Use uniform scoring range (0 – 4)
- Improve instructions and definitions
- Create manual and adapt training tool

Develop Gait & Posture Scale

- Gait and posture are affected early in the disease course
- Impairment of gait and posture is highly relevant for patients

FARS part III section E (upright stability)



1. **Sitting Posture** (Patient seated in chair with thighs together, arms folded, back unsupported; observe for 30 sec.):

   0 - Normal.
   1 - Mild oscillations of head/trunk without touching chair back or side.
   2 - Moderate oscillations of head/trunk; needs contact with chair back or side for stability.
   3 - Severe oscillations of head/trunk; needs contact with chair back or side for stability.
   4 - Support on all 4 sides for stability.

2. **Stance feet apart– Inside of feet 20 cm apart marked on floor. Use stopwatch; 3 attempts; time in seconds):**

   Trial 1 Trial 2 Trial 3 AVG

   0 - 1 minute or longer.
   1 - <1 minute, >45 sec.
   2 - <45 sec., >30 sec.
   3 - <30 sec., >15 sec.
   4 - <15 sec. or needs hands held by assistant/device.

3. **Stance - Feet Together (use stopwatch; 3 attempts; time in seconds):**

   Trial 1 Trial 2 Trial 3 AVG

   0 - 1 minute or longer.
   1 - <1 minute, >45 sec.
   2 - <45 sec., >30 sec.
   3 - <30 sec., >15 sec.
   4 - <15 sec.

4. **Tandem Stance** (use stopwatch; 3 attempts, dominant foot in front; time in seconds)

   Trial 1 Trial 2 Trial 3 AVG

   0 - 1 minute or longer.
   1 - <1 minute, >45 sec.
   2 - <45 sec., >30 sec.
   3 - <30 sec., >15 sec.
   4 - <15 sec.

5. **Stance on Dominant Foot** (use stopwatch; 3 attempts; time in seconds):

   Trial 1 Trial 2 Trial 3 AVG

   0 - 1 minute or longer.
   1 - <1 minute, >45 sec.
   2 - <45 sec., >30 sec.
   3 - <30 sec., >15 sec.
   4 - <15 sec.

6. **Tandem Walk** (tandem walk 10 steps in straight line; performed in hallway with no furniture within reach of 1 m / 3 ft. and no loose carpet):

   0 - Normal (able to tandem walk >8 sequential steps).
   1 - Able to tandem walk in < perfect manner/can tandem walk >4 sequential steps, but <8.
   2 - Can tandem walk, but fewer than 4 steps before losing balance.
   3 - Too poorly coordinated to attempt task.

7. **Gait** (use stopwatch; walk 8 m/25 ft. at **normal pace**, turn around using single step pivot and return to start; performed in hallway with no furniture within reach of 1 m/3 ft. and no loose carpet):

   Device, if any:_____

   Time in seconds:_____

   0 - Normal.
   1 - Mild ataxia/veering/difficulty in turning; no cane/other support needed to be safe.
   2 - Walks with definite ataxia; may need intermittent support/or examiner needs to walk with patient for safety sake.
   3 - Moderate ataxia/veering/difficulty in turning; walking requires cane/holding onto examiner with one hand to be safe.
   4 - Severe ataxia/veering; walker or both hands of examiner needed.
   5 - Cannot walk even with assistance (wheelchair bound).

Subramony et al. Neurology 2005;64:1261-2