

Overcoming Challenges in Registrational Ataxia Trials:

*Balancing the choice of endpoints,
selection of patient population, and
trial duration*

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Key Factors for Designing Registrational Trials

How can we balance all three?



Endpoints: What to Measure?

- Clinical rating scales
- Functional ability tests
- Loss or gain of functional milestones
- Biomarkers
- Wearables
- Patient reported outcomes



Population: Who to Include?

- Age
- Age of first symptoms
- Genetics
- Disease stage/ time from diagnosis
- Functional ability



Duration: How Long Do We Need To Watch?

- How long does it take a scale to change?
- How far apart are functional milestones?



Clinical Outcome Measures in Ataxias

Clinical Rating Scales

- modified Friedreich Ataxia Rating Scale (mFARS)
- Scale for the Assessment and Rating of Ataxia (SARA)
- International Cooperative Ataxia Rating Scale (ICARS)

Functional Assessments

- 1-minute walk test
- Timed up and go
- 9-hole peg test
- Timed 25-foot walk
- Cardiac imaging*

Other Performance Measures

- FARS Activity of Daily Living
- Modified Fatigue Impact Scale
- Columbia Suicide Severity Rating Scale
- Cognitive Assessments
- Speech Assessments

Patient Reported Outcomes

- EQ-5D-5L
- Patient Global Impression Scales
- FA Health Index
- PROM-Ataxia

Biomarkers

- Imaging: MRI and PET
- Neurofilament light (NfL)
- Protein/Gene expression
- Ocular motion
- Cardiac imaging*

Devices and Wearables

- Smart watches
- Pendants
- Pressure Plates/Mats
- iPhone
- Smart utensils

A Clinical Development Perspective on Outcome Measures and How We Choose Endpoints for Clinical Trials

Clinical Rating Scales and Functional Assessments

Pros

- Tend to be more objective and/or timed measures
- Better understood by Regulatory Agencies - Validated
- Represented in NH studies

Cons

- Can take longer to see a benefit
- Hard to translate to clinical meaningfulness

Patient Reported Outcomes/ Other Performance Measures

Pros

- Captures quality of life measures and patient perspective
- Regulatory authorities have put a focus on including these measures
- Important for Market Access and HTA discussions

Cons

- Higher variability
- Still not accepted as primary efficacy endpoints

Biomarkers, Devices, and Wearables

Pros

- More objective measures
- Easier to translate to clinical meaningfulness

Cons

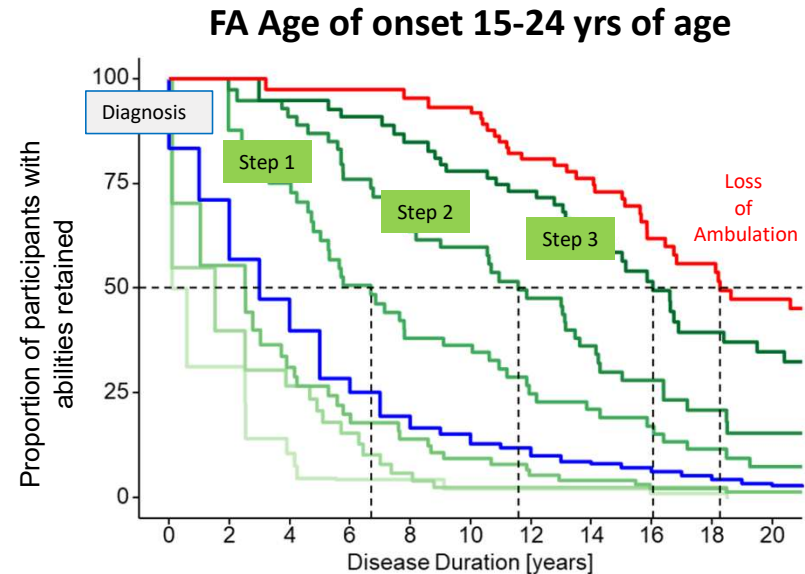
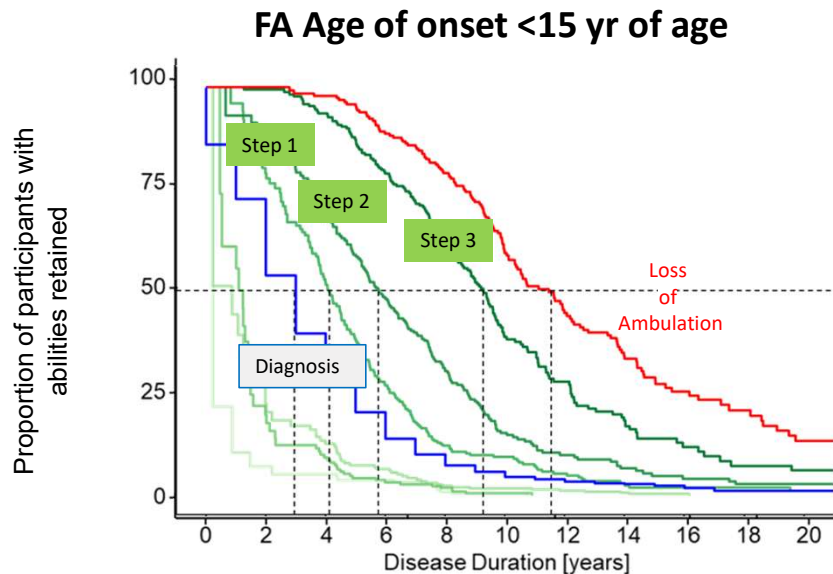
- Most have not been validated
- Not included in NH studies

Considerations for Selection of Endpoints and Patient population

- Focus on the outcome measures that are the most robust and best understood and, ideally, ones that are already accepted and validated by regulatory authorities
- Select endpoints that are appropriate for the patient population selected for the study and the duration of the trial
- Include patient reported outcomes measures to capture aspects of clinical meaningfulness and support market access and HTA
- Don't overload the study with too many assessments
 - This can cause undue burden on site and participants
- Select a homogeneous population – especially in the primary analysis population
 - It is possible to expand inclusion outside primary analysis population

Who to Include? *Age of symptom onset*

Including both populations can make it harder to see a treatment benefit in the overall trial – consider how endpoints are impacted by age/ disease stage

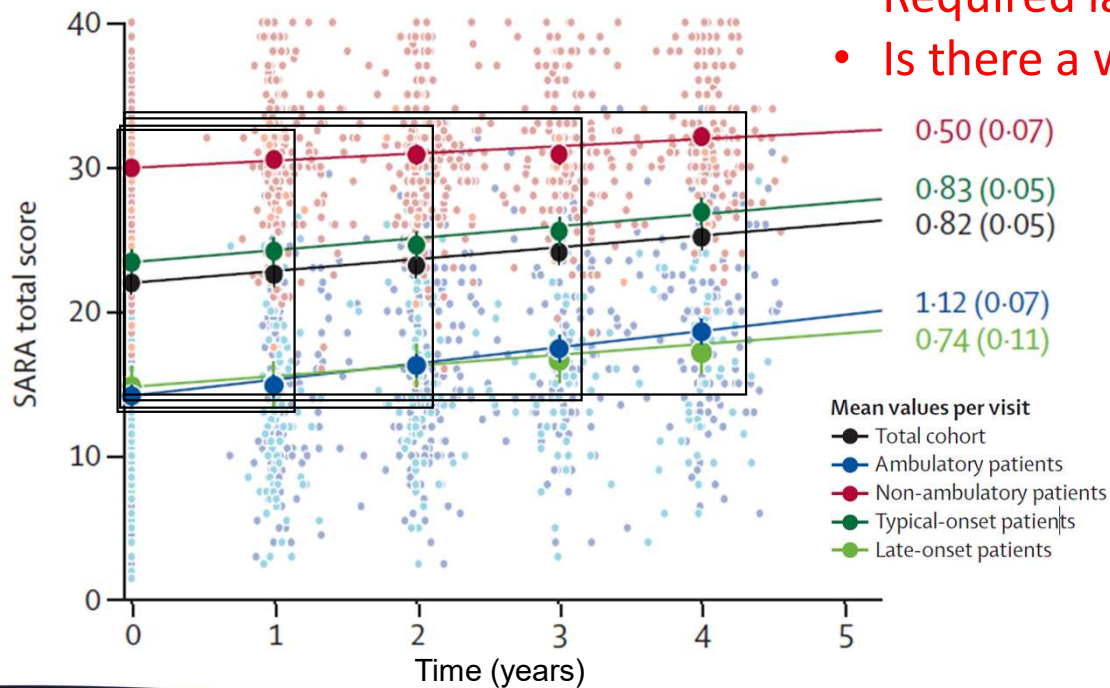


- Earlier onset leads to more rapid progressive disease – in this case loss of ambulation
- Onset in young adults also results in less occurrence of scoliosis and cardiomyopathy

How Long Does a Trial Need to Be? *Rate of Disease Progression*

Annual progression rate is statically significant but...

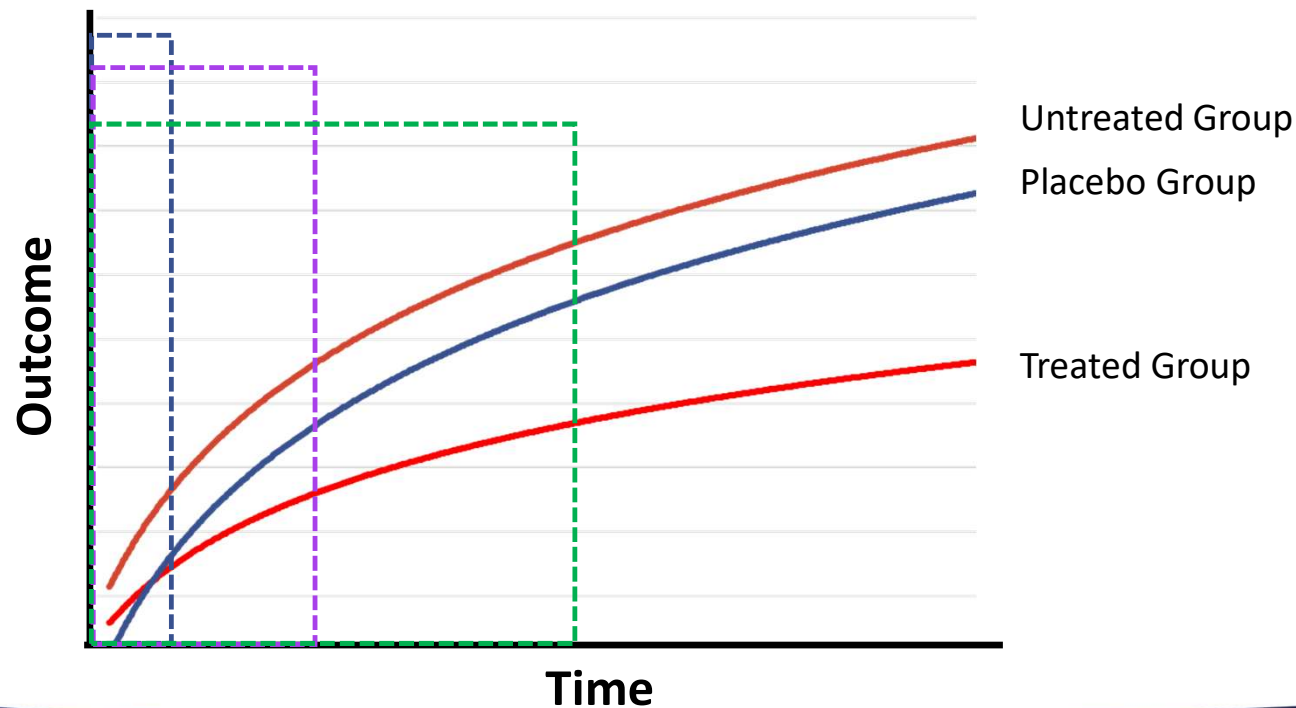
- Variability is high
- Required large numbers of patients over many years
- Is there a window to detect clinical benefit?



Mean change in SARA score over time			
Years	Total EFACTS cohort	Ambulatory Patients	Non-Ambulatory Patients
1	0.59	0.72	0.58
2	1.2	2.11	0.91
3	2.12	3.26	0.94
4	3.15	4.36	2.16

How Long Does a Trial Need to Be? *Placebo Effect*

Too short and the results can be impacted by placebo effect
Too long and the trial cost and burden on patients can be too high



Parameters for a registrational trial are predefined and aligned with regulatory authorities before the study starts.

- When you start a trial, you must predict what endpoints will change, how they will change, and how long it will take.
 - This defines the parameters for the trial, including number of patients, duration, and primary endpoint
- This is done using what we know about disease progression from natural history data and other clinical trials.
- If you pick wrong, there is a chance you can miss your primary endpoint which could result in a failed trial.

- What happens when our understanding changes and new data on disease stage and progression occurs while you are running the study?

Conclusion

Registration trial design need to balance

- i. patient population
- ii. disease stage
- iii. appropriate clinical assessment measures

and have a duration that allows enough time to observe and clinically meaningful and statistically significant benefit.