

Activities of Daily Living

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Types of Patient Reported Outcomes

- Health-related quality of life (HRQL)
multidimensional; generic or disease specific (e.g., SF-36)
- Functional status
ability to perform both basic and more advanced activities of daily life
- Symptom specific scales
specific to types of symptom (fatigue, pain intensity, etc.)
- Health behaviors
specific to types of behaviors (smoking, drug use, physical activity, food consumption)
- Patient experience of Care

The FA-ADL

- Subramony, May, Lynch, Gomez, Fischbeck, Hallett, Taylor, Wilson, Ashizawa
Measuring Friedreich's Ataxia, *Neurology* **2005**
- “modelled after existing scales for e.g., ALS”
- 9 items, to be scores 0-4
(normal/mild/moderate/severe/unable)
- Total Score of 36 (higher is worse)

ADL

Speech

Swallow

Food

Dress

Hygiene

Fall

Walk

Sit

Bladder

ADL

Speech

Swallow

Food

Dress

Hygiene

Fall

Walk

Sit

Bladder

6. Falling (assistive device = score 3)

0 - Normal.

1 - Rare falling (< once a month).

2 - Occasional falls (once a week to once a month).

3 - Falls multiple times a week or requires device to prevent falls.

4 - Unable to stand or walk.

7. Walking (assistive device = score 3)

0 - Normal.

1 - Mild difficulty, perception of imbalance.

2 - Moderate difficulty, but requires little or no assistance.

3 - Severe disturbance of walking, requires assistance or walking aids.

4 - Cannot walk at all even with assistance (wheelchair bound).

8. Quality of Sitting Position

0 - Normal.

1 - Slight imbalance of the trunk, but needs no back support.

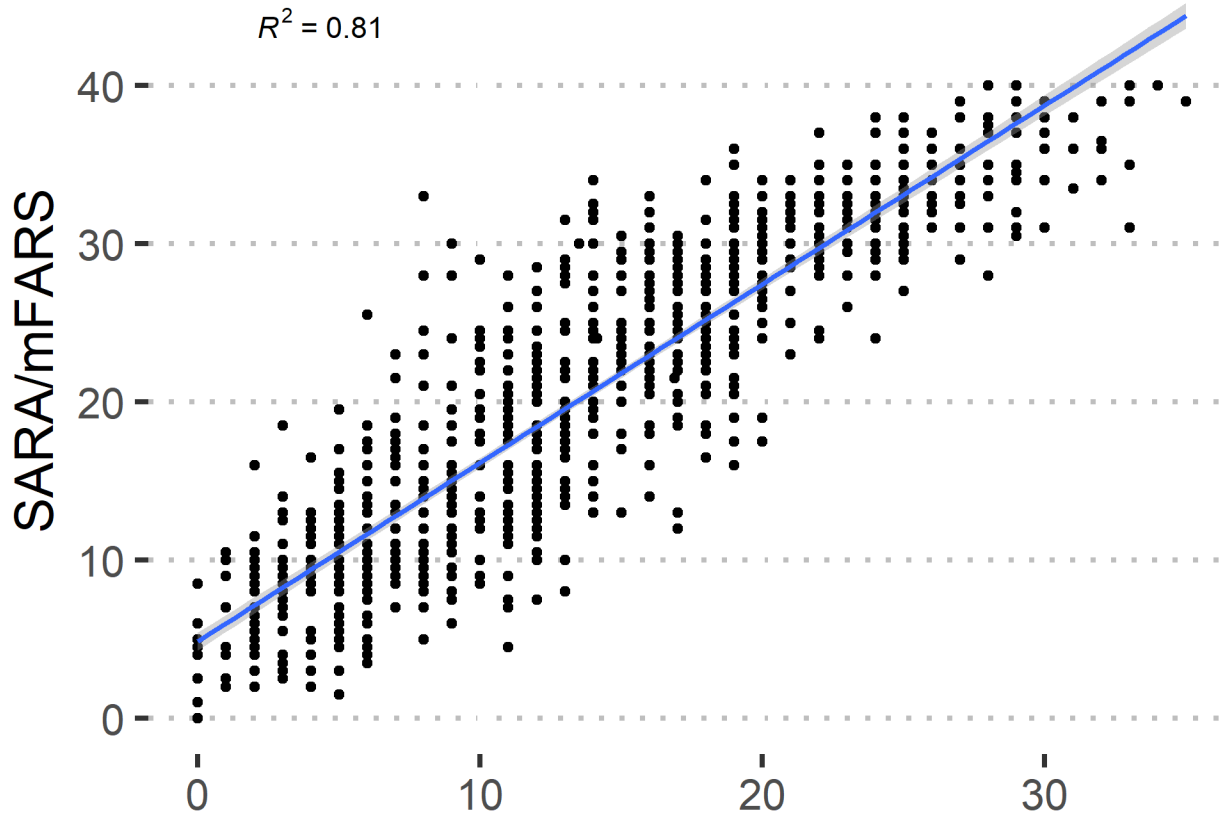
2 - Unable to sit without back support.

3 - Can sit only with extensive support (Geriatric chair, posy, etc.).

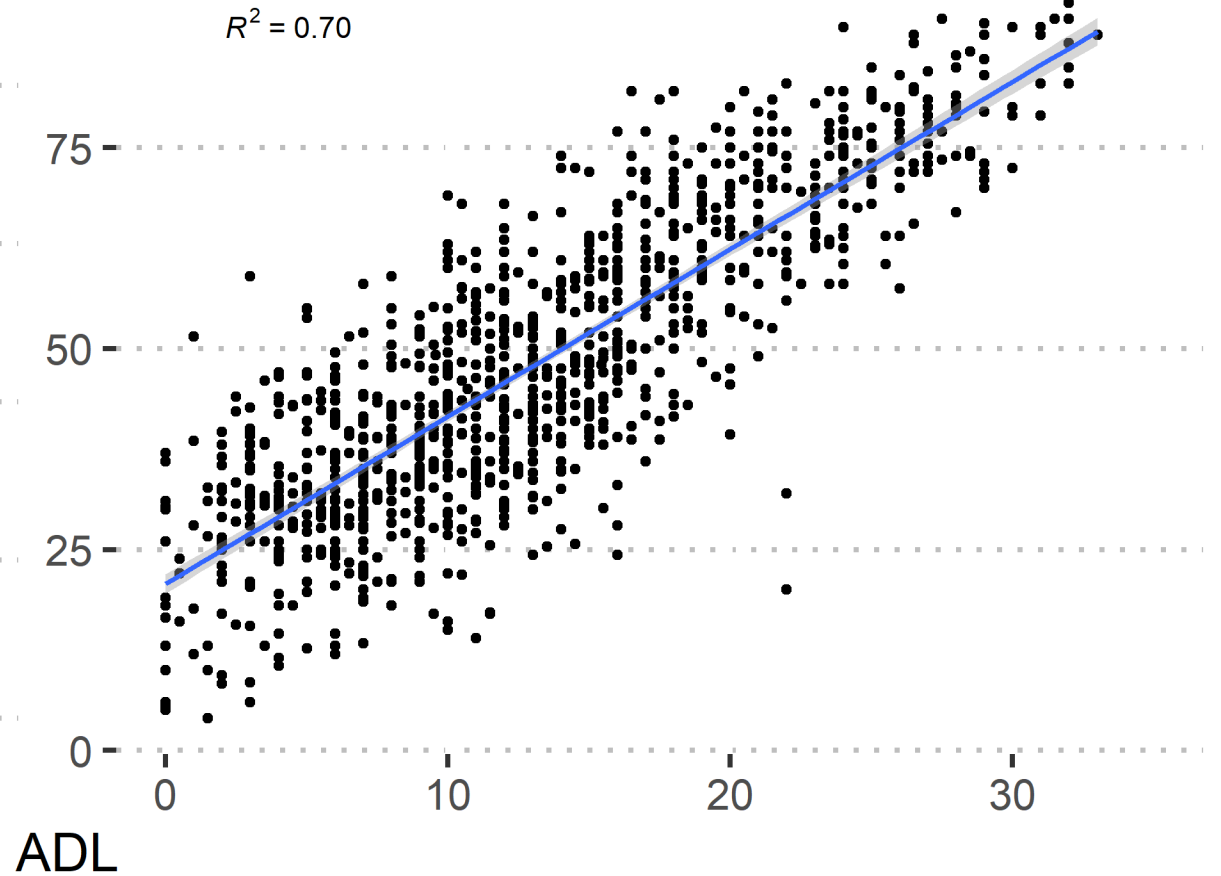
4 - Unable to sit.

Correlations ADL vs SARA / mFARS

EFACTS



FACOMS



ADL (36)

Speech
Swallow
Food
Dress
Hygiene
Fall
Walk
Sit
Bladder

SARA (40)

Speech 1 (6)
Upper limbs 3 (12)
Heel shin 1 (4)
Gait 3 (18)

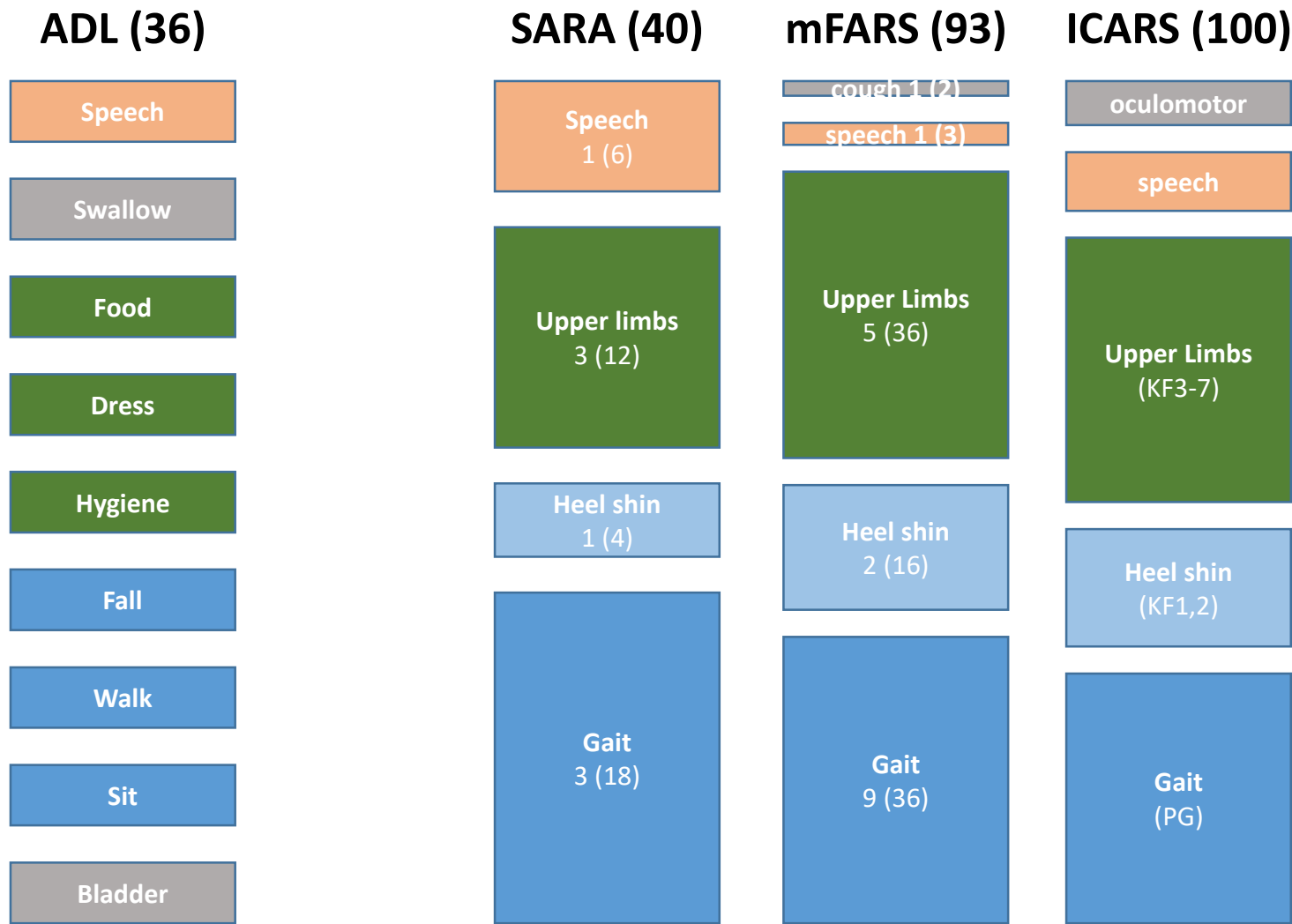
mFARS (93)

cough 1 (2)
speech 1 (3)
Upper Limbs 5 (36)
Heel shin 2 (16)
Gait 9 (36)

ICARS (100)

oculomotor
speech
Upper Limbs (KF3-7)
Heel shin (KF1,2)
Gait (PG)

Comparison of Domain Weights in FA Rating Scales



Use in Clinical Trials

IONIA (idebenone, 2008/2009)

- Phase III Trial using ICARS as primary outcome measure
- 6-months treatment duration
- Results: Trend but no significance
- ADL result closely resembled the FARS / ICARS result

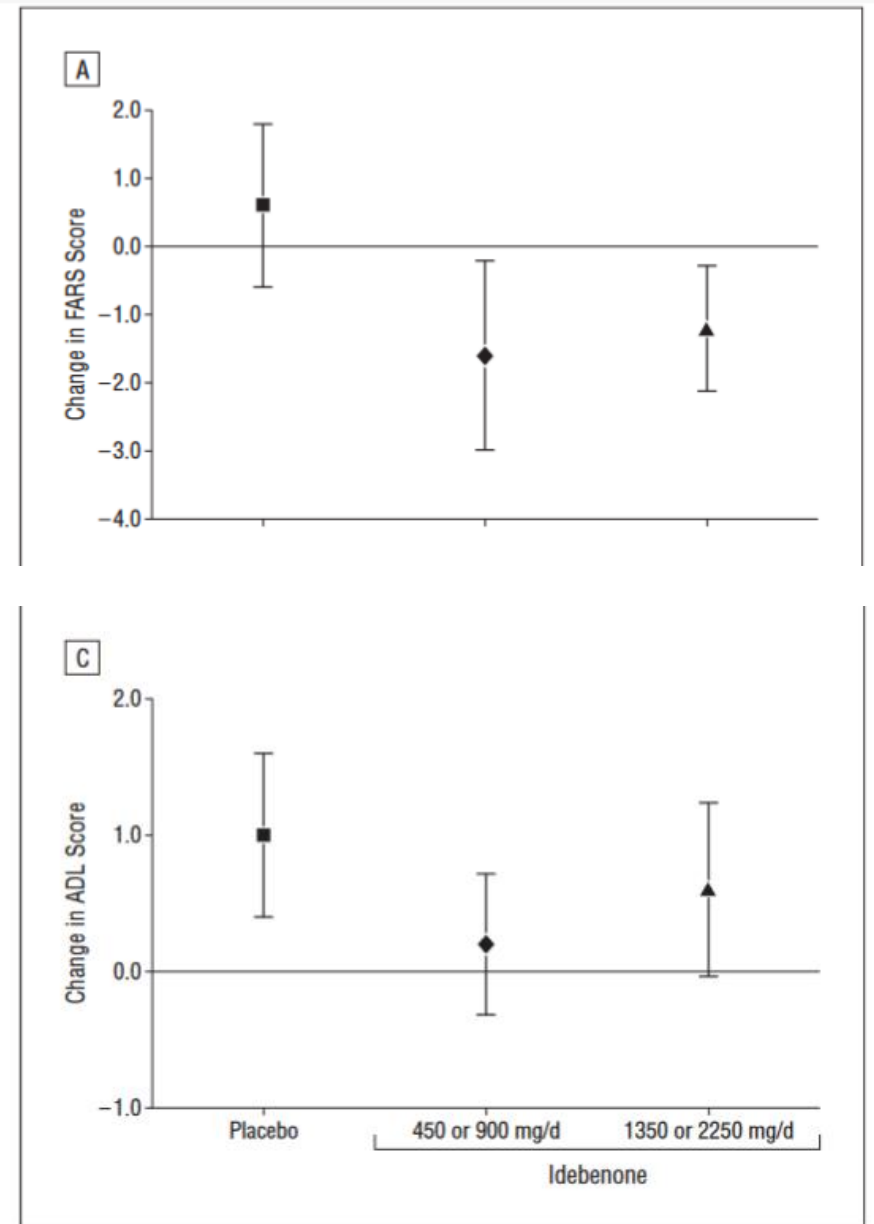


Figure 4. Mean changes between week 24 and baseline for the secondary efficacy parameters. ADL indicates activities of daily living; FACT-Z₃, Friedreich's Ataxia Composite Test; and FARS, Friedreich Ataxia Rating Scale. Error bars represent the standard error of the mean.

Deferiprone (2014)

- Phase II Trial using ICARS as primary outcome measure
- 6-months treatment duration
- Result: high dose showed worsening in ataxia
- ADL result closely resembled the FARS / ICARS result

Table 3. Efficacy outcomes at the end of study

	Intent-to-Treat (ITT) Population without 60 mg Dose group		
	Placebo	Deferiprone	
		20 mg/kg/day	40 mg/kg/day
Change in FARS total score from baseline			
N	11	21	20
Mean \pm SD	-0.8 \pm 5.4	-0.5 \pm 5.6	6.2 \pm 6.8
P value†		0.8047	0.0018
Change in ADL score from baseline			
N	11	21	20
Mean \pm SD	-0.5 \pm 2.4	-0.0 \pm 3.4	2.6 \pm 3.0
P value†		0.5222	0.0044

MOXIE / Omaveloxolone

A

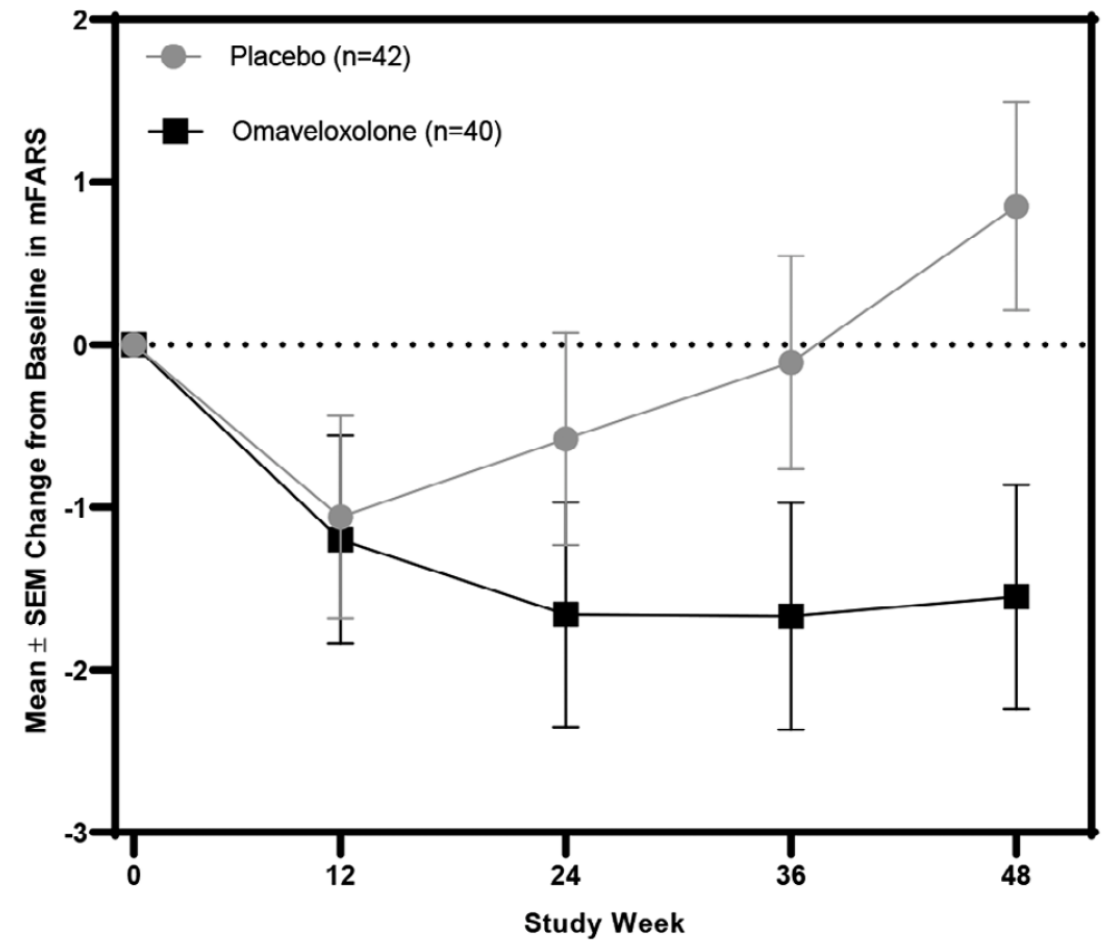


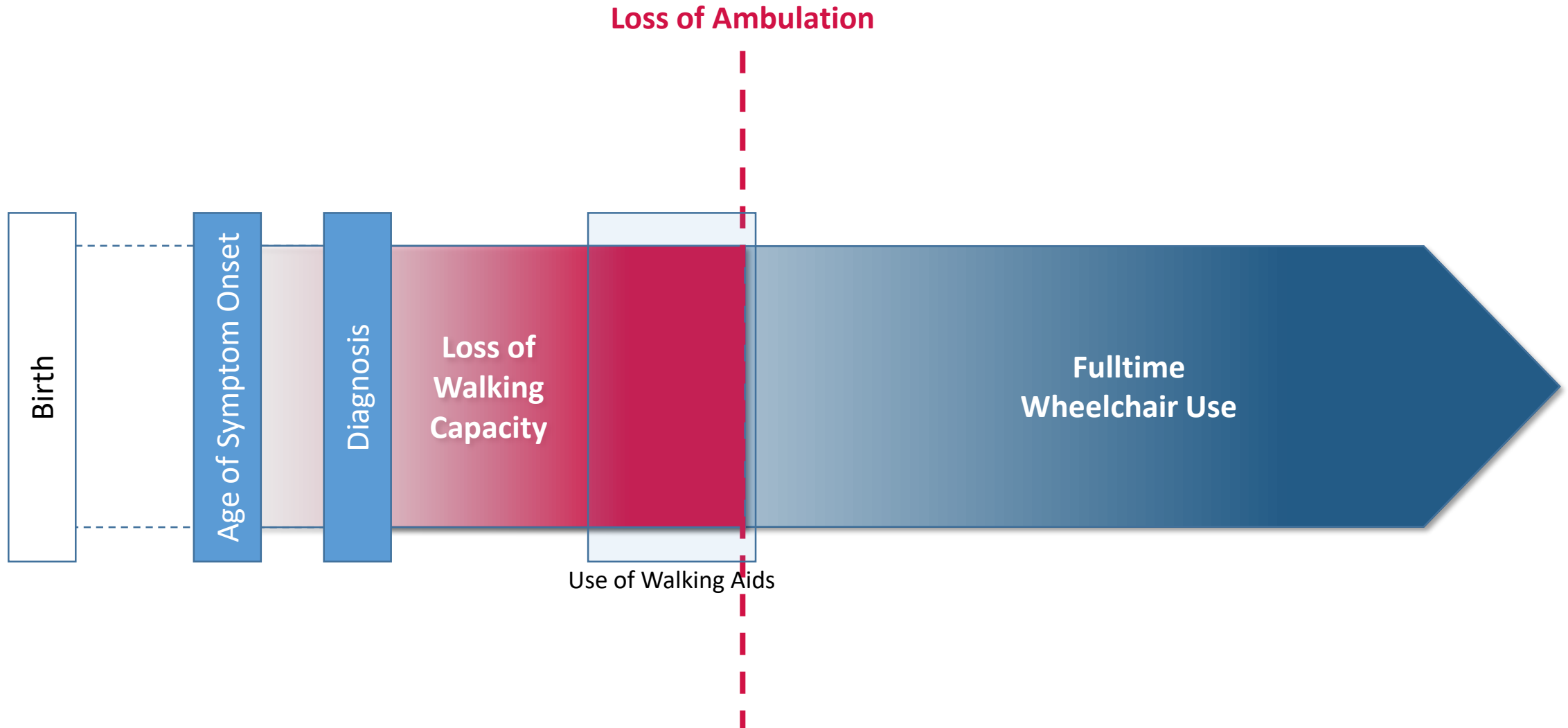
TABLE 2. Secondary Endpoints and Post Hoc Analyses of Proportion of Patients Who Improved or Worsened in Primary and Secondary Measures at Week 48

Endpoint	Week 48 Change from Baseline ^a		Mean Difference ± SEM between Treatment Groups
	Placebo, n = 42	Omaveloxolone, n = 40	
PGIC	4.33	3.90	-0.43, <i>p</i> = 0.13
CGIC	4.06	3.93	-0.13, <i>p</i> = 0.52
FA-ADL	1.14 ± 0.42, <i>p</i> = 0.009	-0.17 ± 0.450, <i>p</i> = 0.71	-1.30 ± 0.629, <i>p</i> = 0.04

ADL in clinical trials

- closely resembles rating scale results**
- slightly less powerful / sensitive**

Disease Course of (Friedreich's) Ataxia

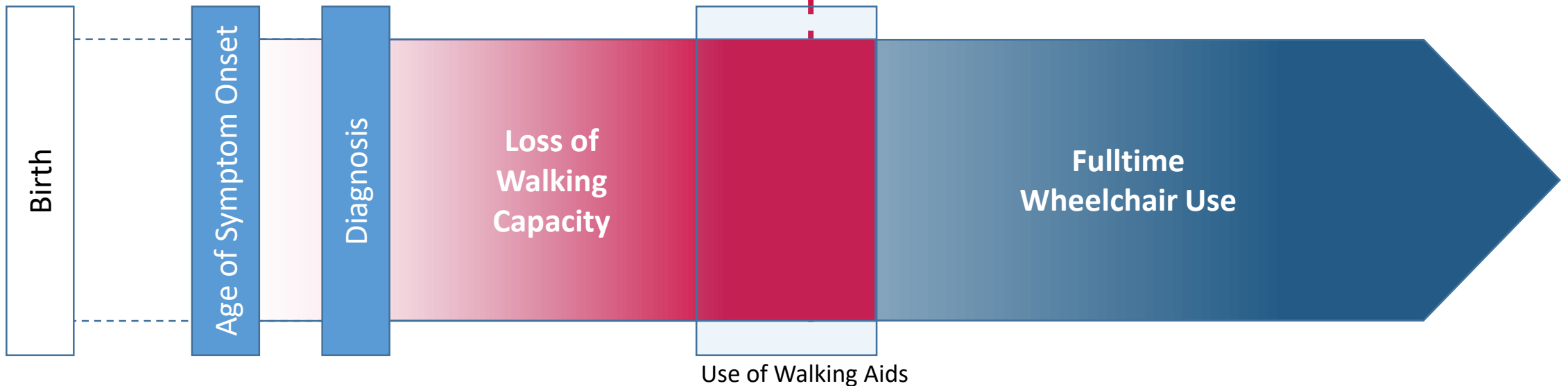


Outcome Measures

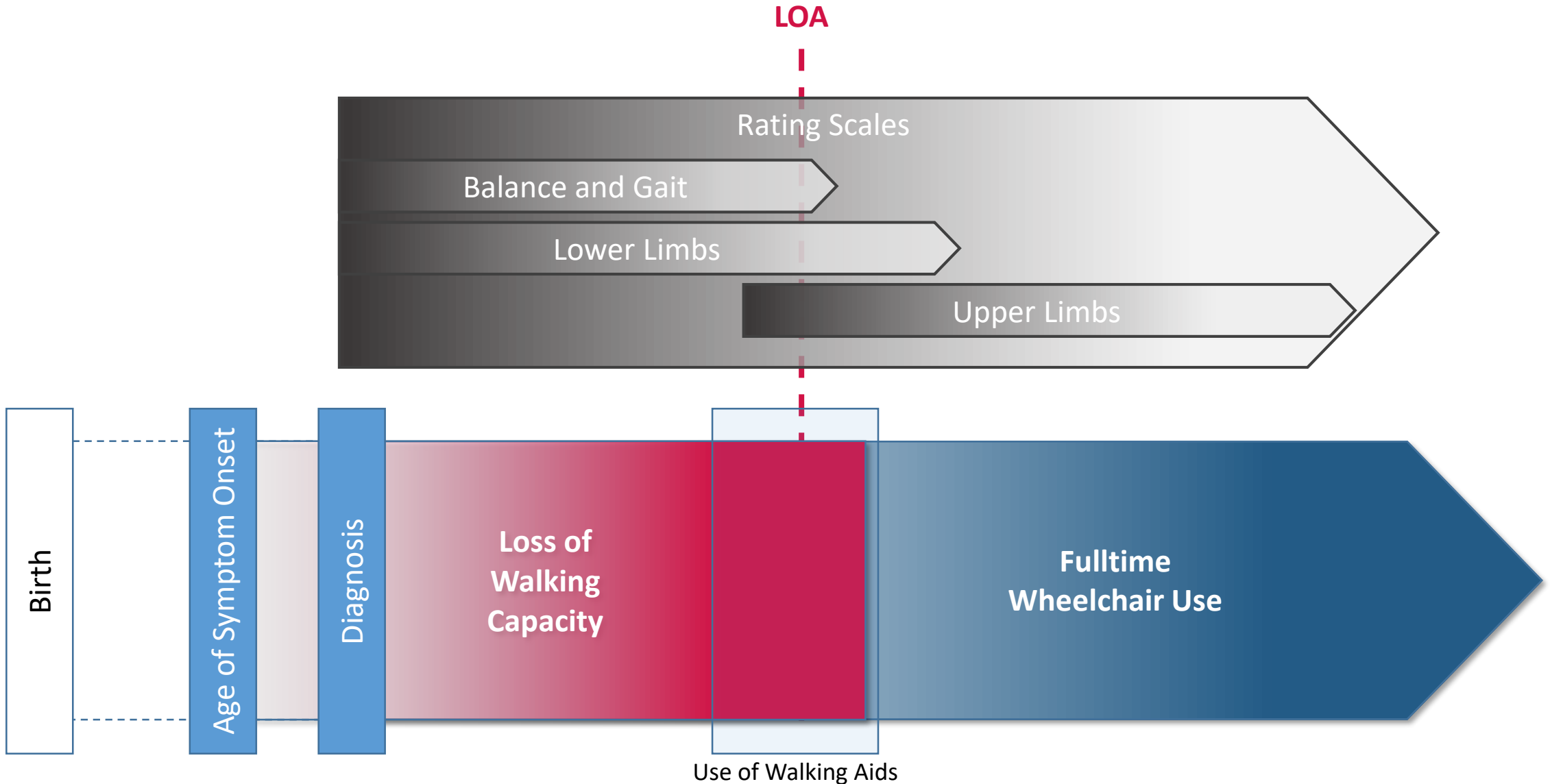
- Rating Scales
 - mFARS / SARA
 - FARS.E (upright stability)
- Activities of Daily Living
- Timed Measures
 - 25-Foot Walk (1MW, etc.)
 - 9-HPT
- Disease Staging

LOA

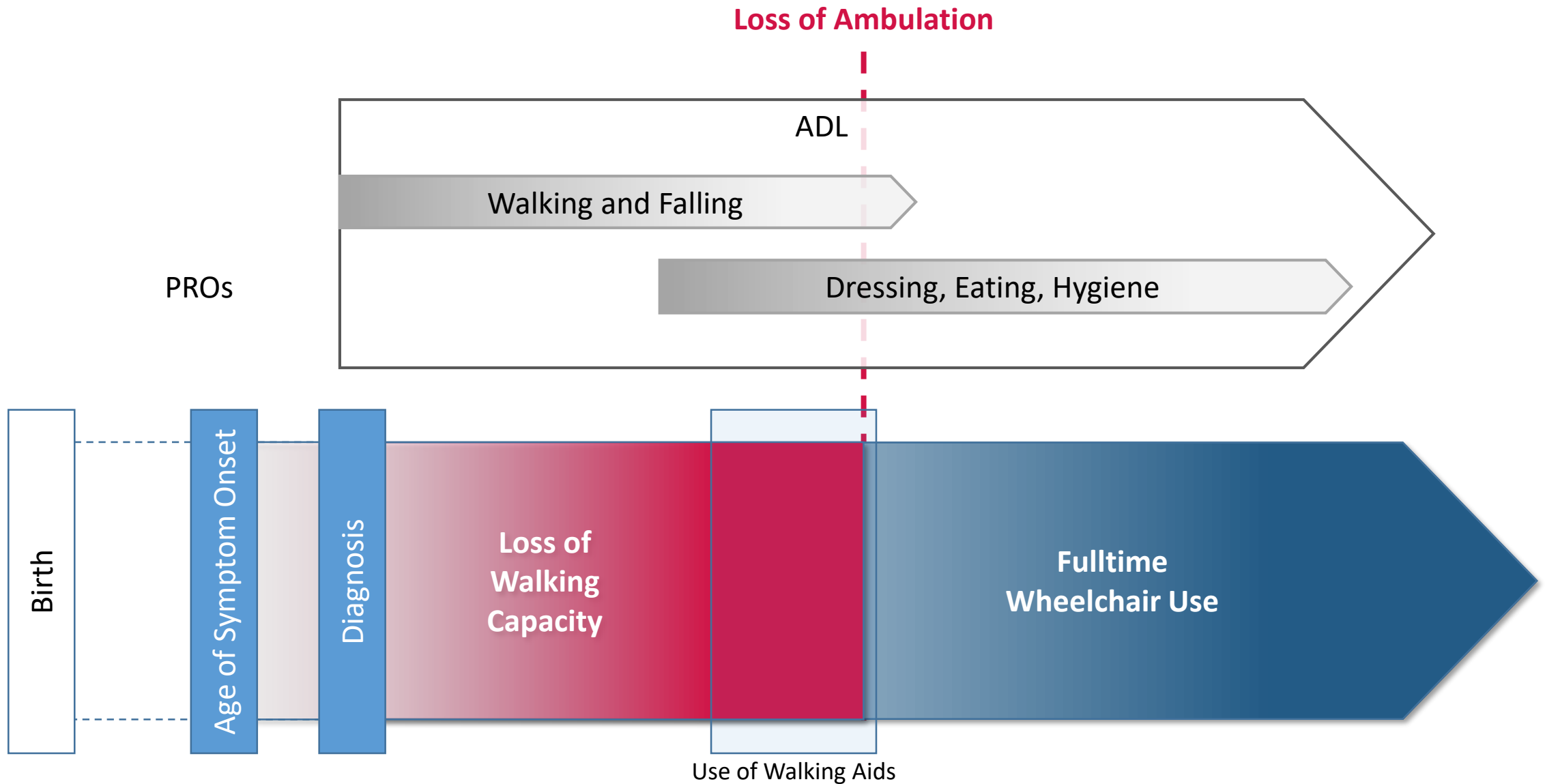
- Rating Scales
 - FARS B / FARS C
- Activities of Daily Living
- Timed Measures
 - 9-HPT



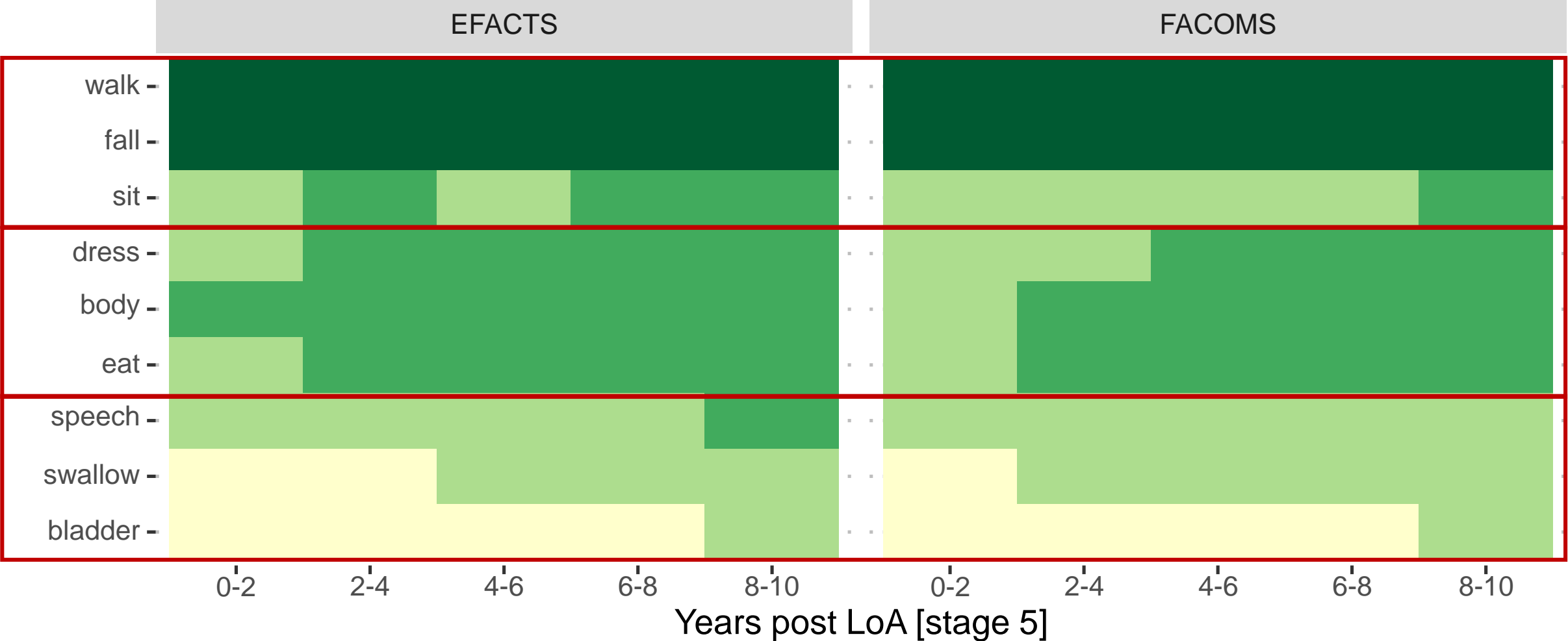
Outcome Measures, relative to Disease Phases



Outcome Measures, relative to Disease Phases



ADL Scores after LoA

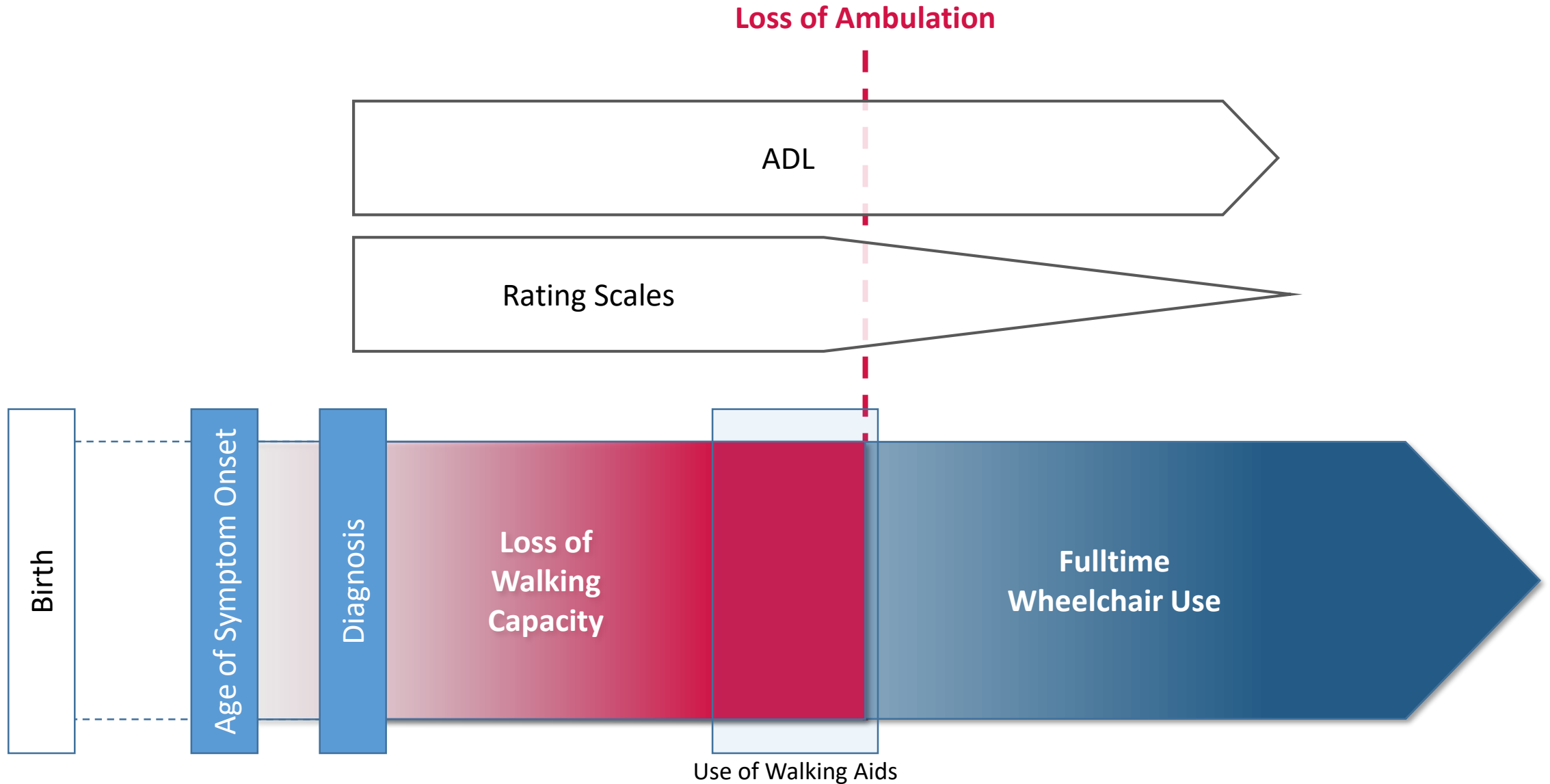


ADL Sensitivity in non-ambulatory populations

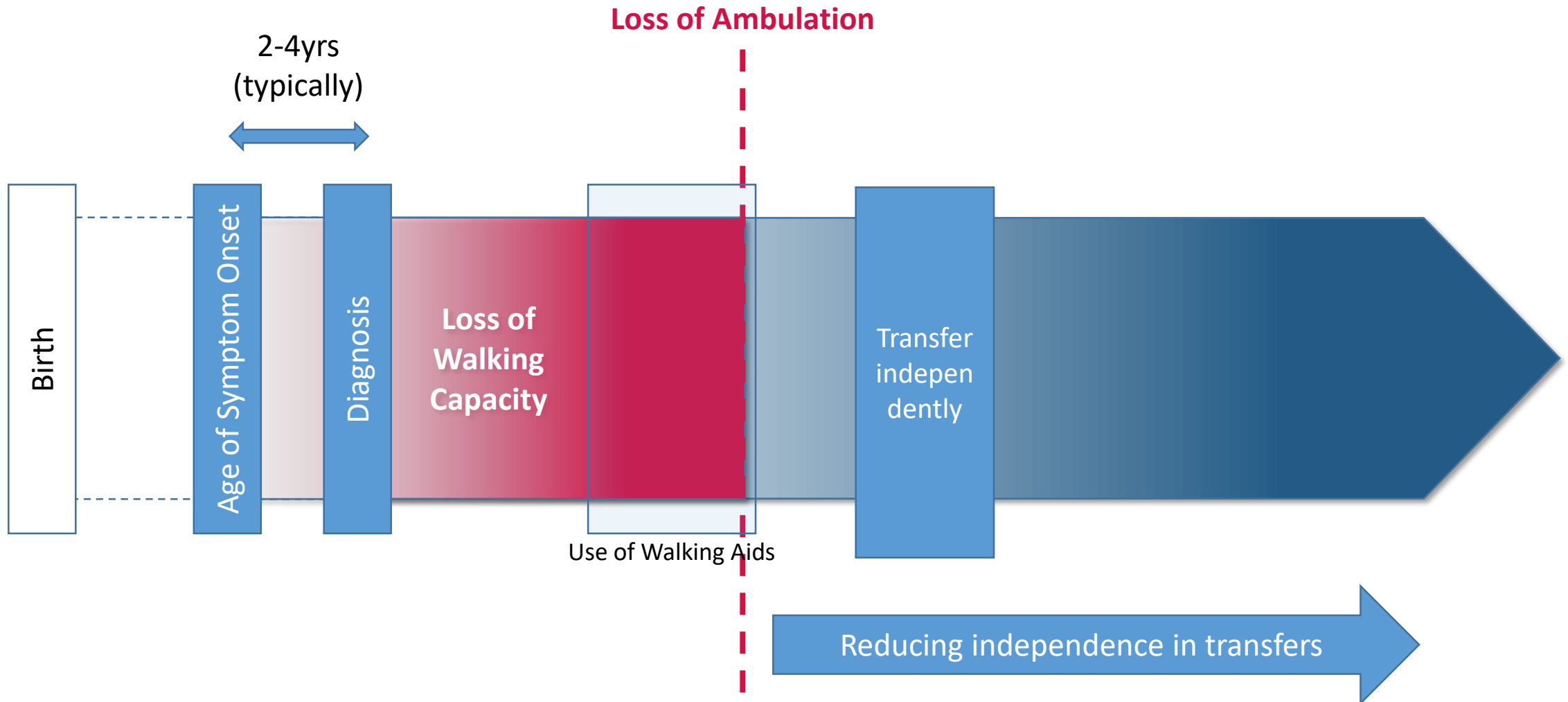
- EFACTS: Reetz et al, 2021

ADL assesses the functional status in Friedreich's ataxia with relatively high responsiveness and sensitivity to change of almost one point per year.⁵ Although progression rates vary with earlier symptom onset, ADL is also able to capture disease progression in wheelchair users with similar sensitivity. The usefulness of functional scales to monitor disease progression in later stages of Friedreich's ataxia and applicability in interventional trials has already been shown with other instruments, such as the Functional Independence Measure.^{25,28} In contrast to SARA, ADL has fewer items focusing on lower limb coordination, yet additional items not covered by SARA measure everyday abilities (eg, cutting food, dressing) and functions (ie, bladder function, dysphagia) showing higher rates of progression after ambulation is lost. Strongest effects were observed for the subitem falls with a higher progression rate in patients with typical onset. As falls are one of the most frequently reported features of the disease,² systematic assessment of these disturbances is of clinical relevance. Thus, different items of the ADL related to specific body functions complement SARA and highlight its capacity to monitor progression across disease stages. Notably, as a patient-reported outcome, ADL is also an easily applicable instrument of functional impairment,

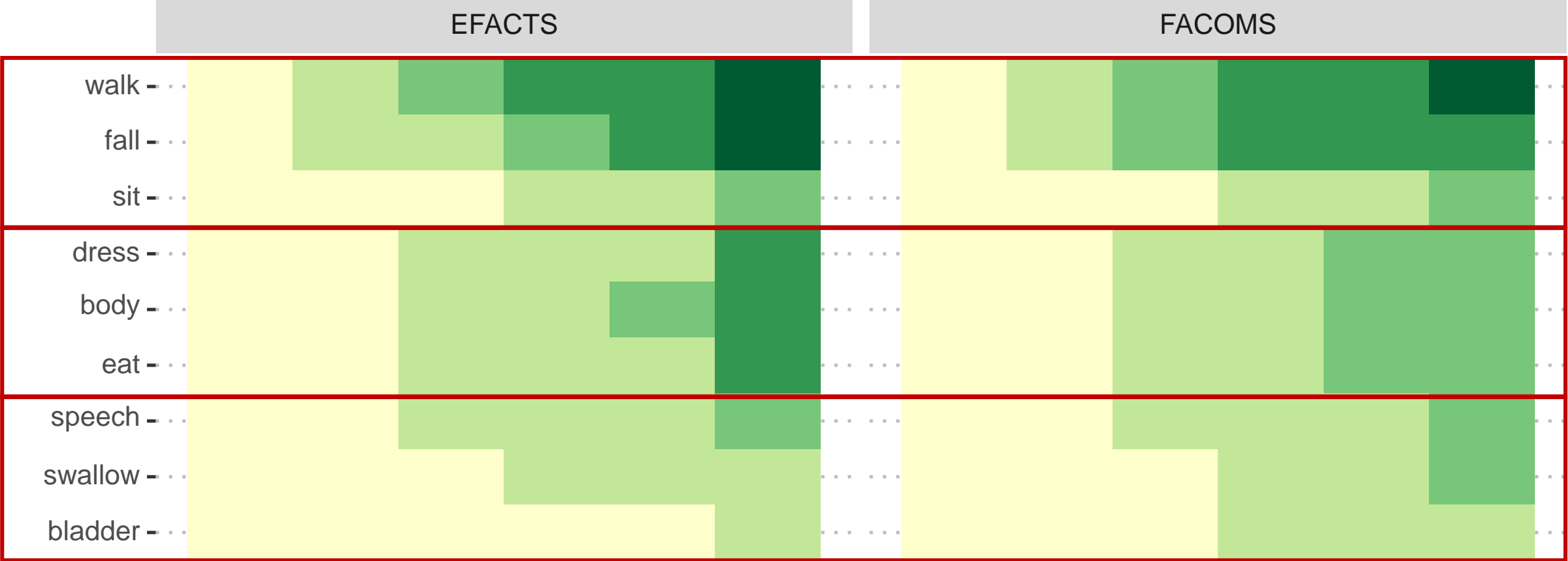
Outcome Sensitivity



Defining clinically relevant milestones...



ADL Scores by Disease Stage



Disease Staging (5=non-ambulatory)

FA-HI
PROM-Ataxia

FA-ADL

Symptoms
(fatigue, vision, pain, ...)