Regulatory approval of digital outcome : Experience in Duchenne, and first step in MS

Margaux Poleur, Alexis Tricot, Damien Eggenspieler, Dimitri Lozeve, Alexandra Goodyear, Paul Strijbos, Laurent Servais

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Muscular Dystrophy UK
Fighting muscle-wasting conditions
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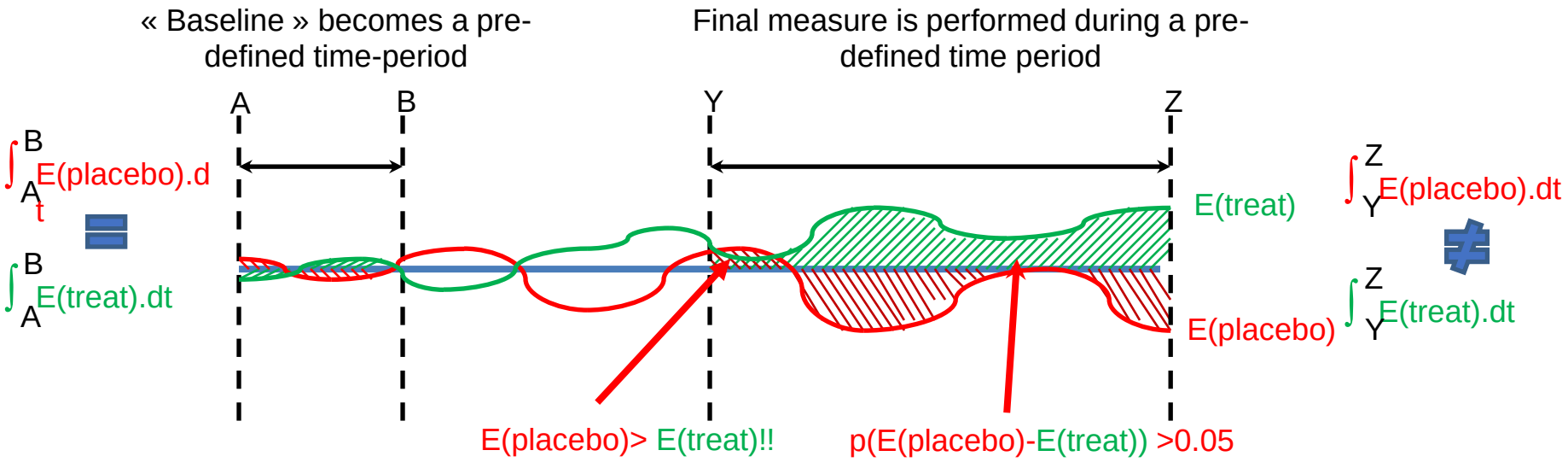
Background

Clinical Gold Standard → New Biomarker Qualification

Major challenges of current state (1)

All measures performed in the hospital, it remains a single point assessment, and highly dependant on patient's form and motivation



Background

Clinical Gold Standard → New Biomarker Qualification

Major challenges of current state (3)

Patients with rare disease may travel
a lot to access the research center

To evaluate patients with wearable devices is just the sense of History. The only question that remains is how long we need to undestand that it is a much more robust solution than hospital-based assesments

The Rapid Evolution of Digital Endpoints: Are We Headed in the Right Direction?

The number of unique digital endpoints being used in industry-sponsored trials of new medical products is skyrocketing, but is more always better?

Jennifer Goldsack Follow

Jan 26 · 6 min read

Just over a year ago, we launched our crowdsourced library of digital endpoints, aiming to shine a light on digital measures being used in industry-sponsored trials and galvanize the field around specific measures to speed adoption. During our most recent update of the library, we were struck by the astronomical growth of digital endpoints over such a short time span.

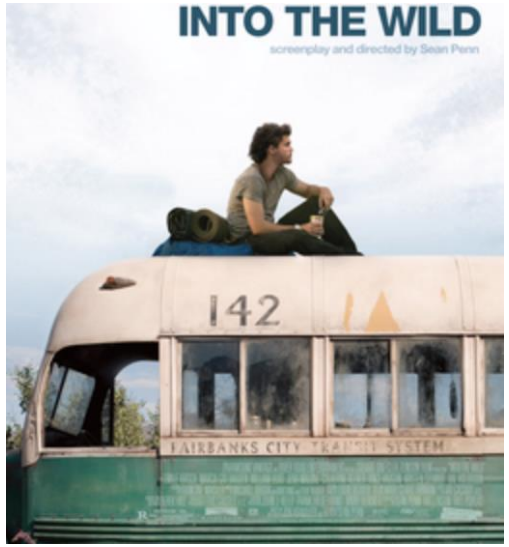
Let the numbers speak for themselves:

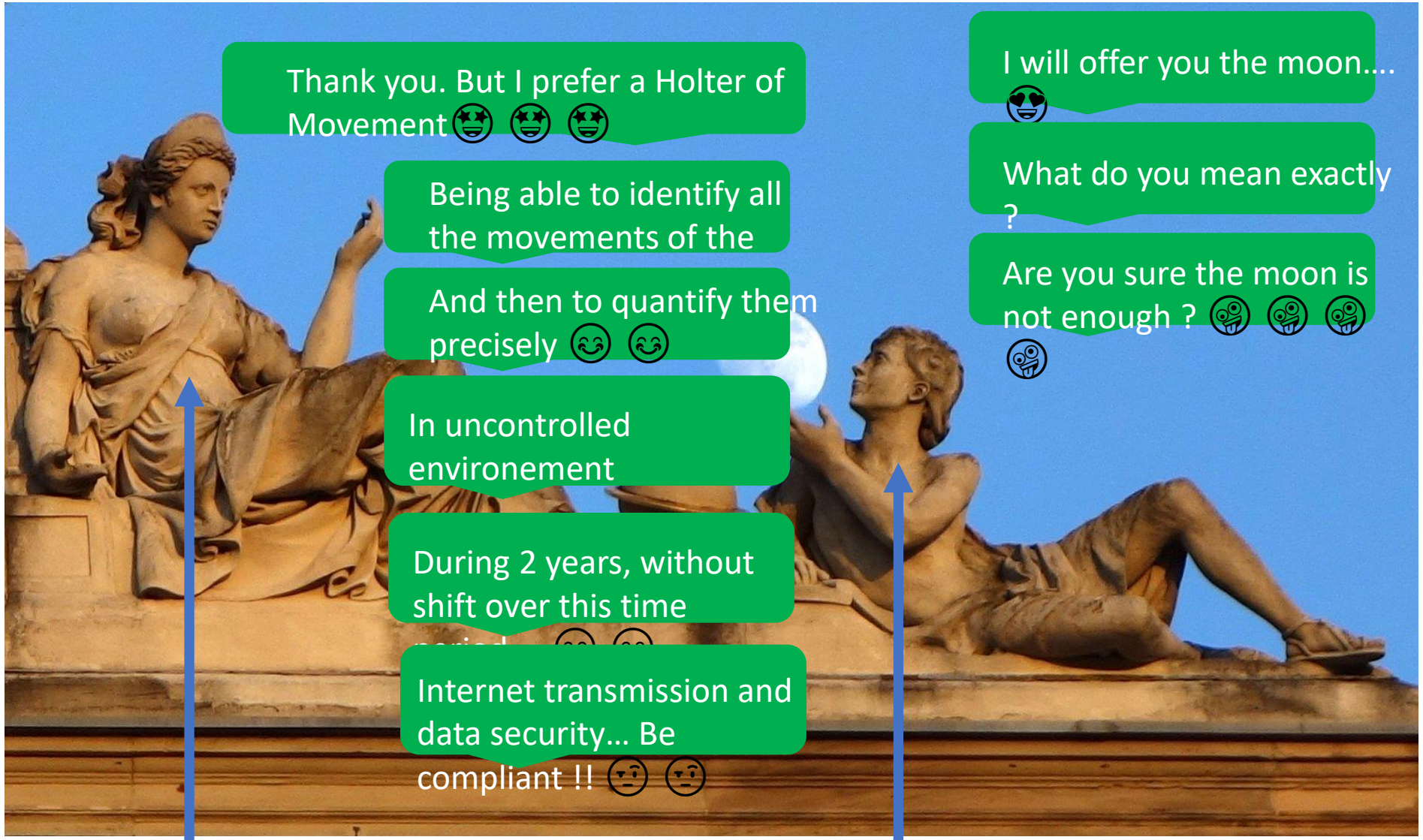
- The number of **unique digital endpoints** increased from **34 to 166 in the last 14 months**, and the number of **sponsors** actively collecting digital endpoints in clinical trials of their medical products has **increased from 12 to 52**.

So why are wearable devices not more used as primary outcome ??

What can I do with that ??

Clinical trial





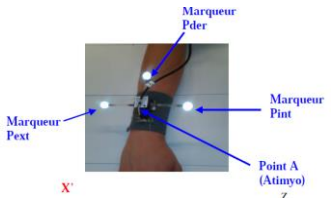
The doctor

The engineer

The long and winding road of SV95C

Technical development timeline

Controlled environment —> unsupervised usage



2010

Identification of the variables

Prototype

V2.0

2011

Validation during NHS

V3.0

2012

Medical device

2017

Clinical trial

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SCIENCE MEDICINES HEALTH

2019

What do we need??

2021

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2022

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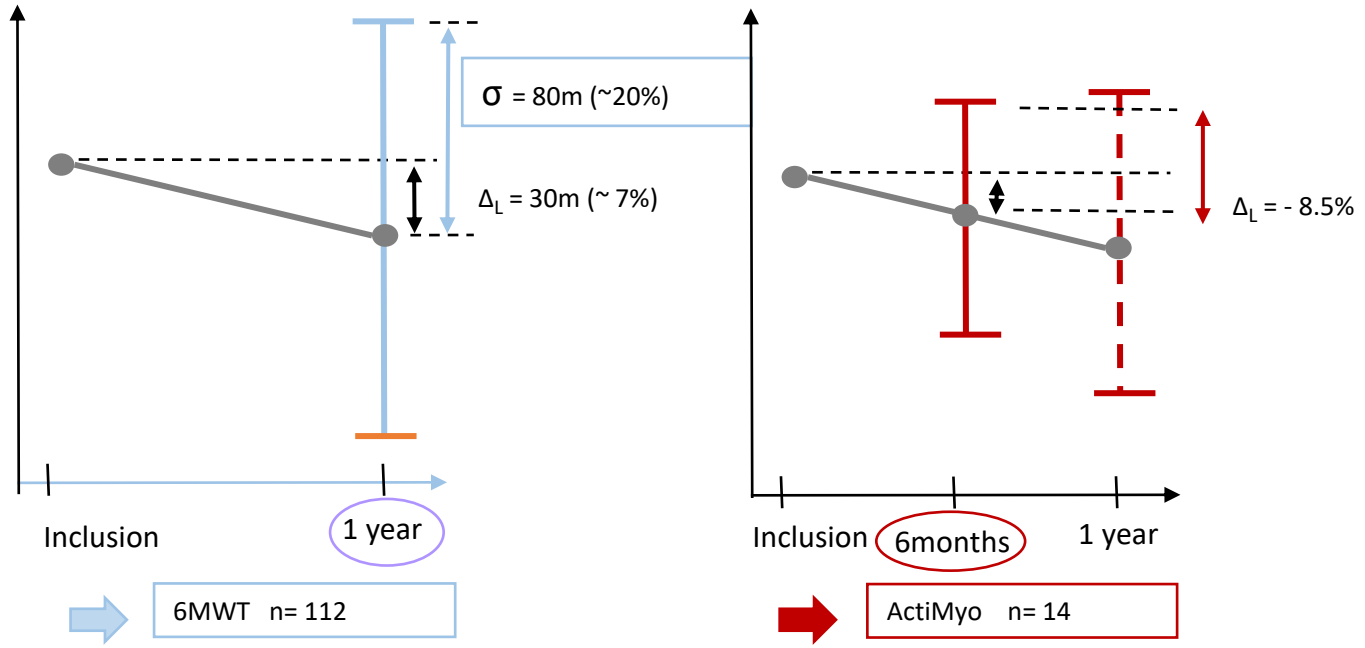
DMD add on value

$$n = \frac{2\sigma^2}{\Delta_L^2}(z_{1-\alpha} + z_{1-\beta})^2$$

Risk α = probability to wrongly conclude to treatment efficacy
=> α : 5% Z= 1.96
Risk ß = probability to wrongly conclude to treatment inefficacy
=> ß : 20% Z= 0.842



2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018
Adopted by CHMP	26 April 2019

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

2023

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2023

Case No.: EMA/SA/0000083386

Committee for Medicinal Products for Human Use (CHMP)

Draft Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies

Draft agreed by Scientific Advice Working Party (SAWP)	01 September 2022
Adopted by CHMP for release for consultation	15 September 2022[1]
Start of public consultation	28 February 2023[2]
End of consultation (deadline for comments)	10 April 2023

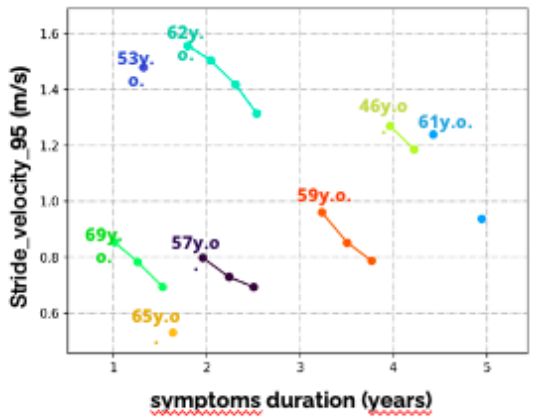
Comments should be provided using this template. The completed comments form should be sent to ScientificAdvice@ema.europa.eu

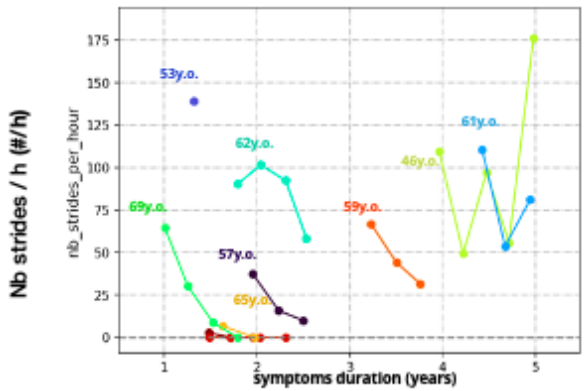
Keywords	Qualification of Novel Methodology, Duchenne Muscular Dystrophy studies, Digital Health Technology, efficacy endpoint, wearable sensor

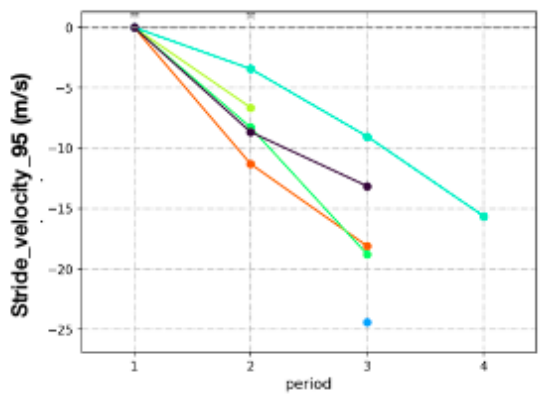
Extension to other diseases… ALS

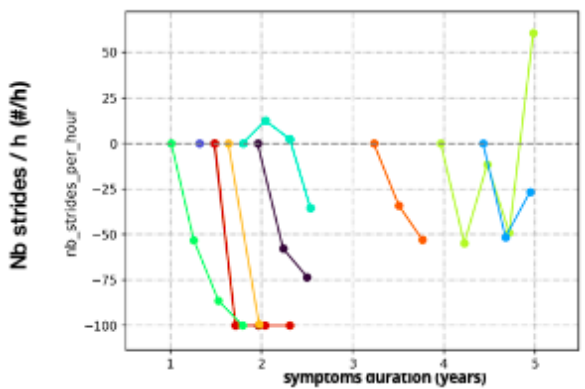
The SV95C is a very robust outcome, because does rely less on motivation & patient environment

Longitudinal evolution of untreated ALS patients measured with SV95C (left, in m/s) and # of strides per hour



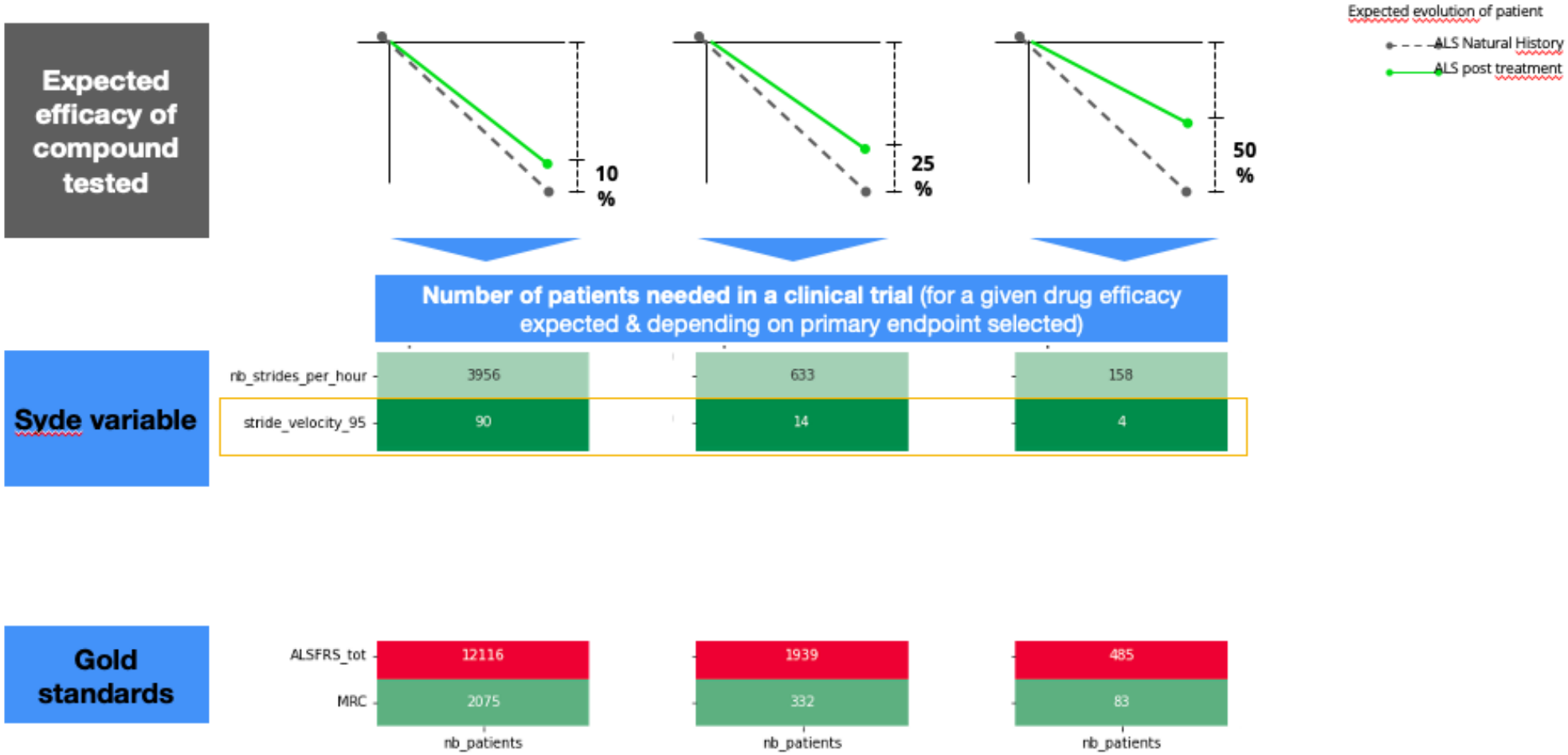






Extension to other diseases… ALS

With the SV95C, we need 20 times less ALS patients to power a clinical trial compared to traditional gold standard



ActiMS : one project, two study protocols

Controlled environment

Aim: ***Analytical*** validity

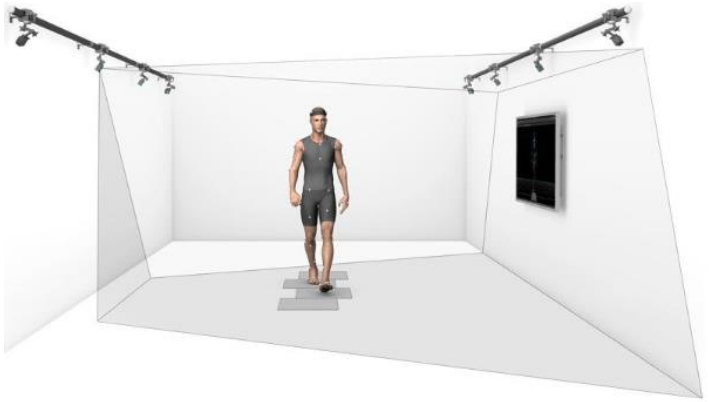
- Validate stride algorithms in this context of use & patient population:
  - **Stride detection** is specific & selective
  - **Stride reconstruction** is precise & accurate
- Elaborate additional capabilities:
  - suitable algorithms for specific MS clinical manifestations (ataxia, spasiticity, asymmetry).

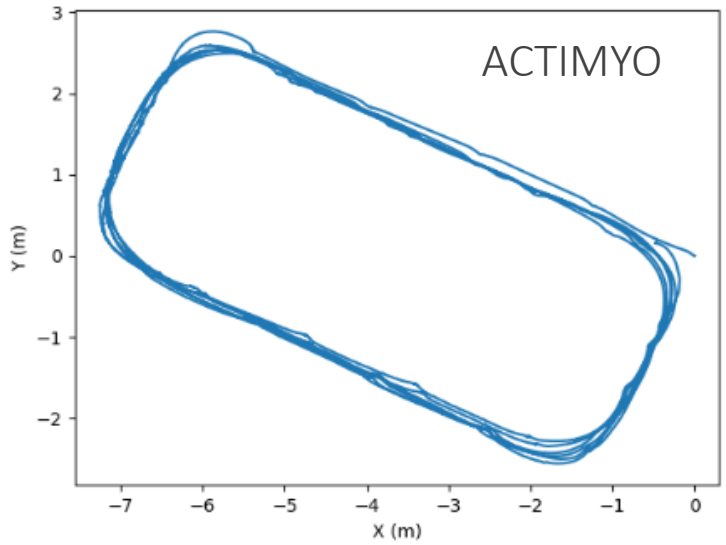
Non-controlled environment

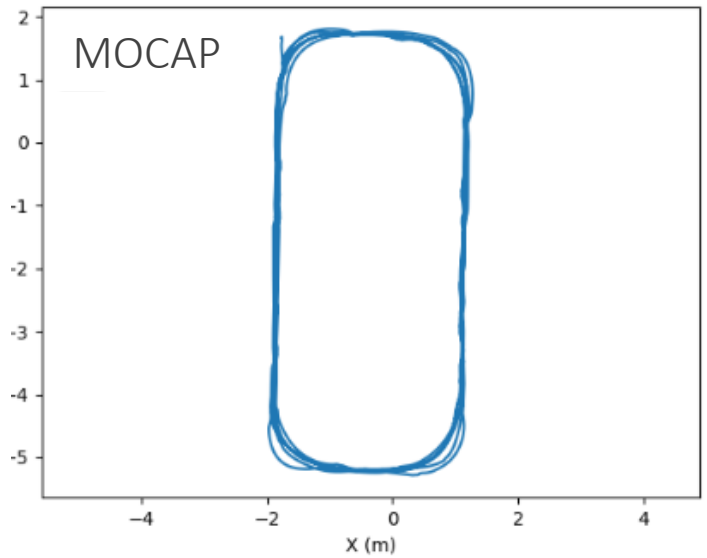
Aim : Feasibility to assess MS real life function & early sign of endpoint ***clinical validity***

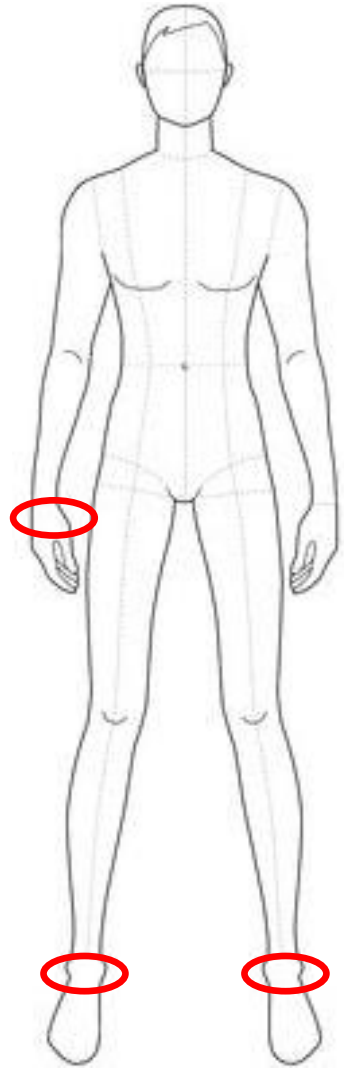
- Evaluation of non specific measures (95SVC, walking perimeter):
  - Concurrent validity
  - Robustness
  - Measure sensitivity to change
- Establishing disease agnostics measure (eg spasiticity, ataxia, etc. in real-life)
  - 1st results

Population







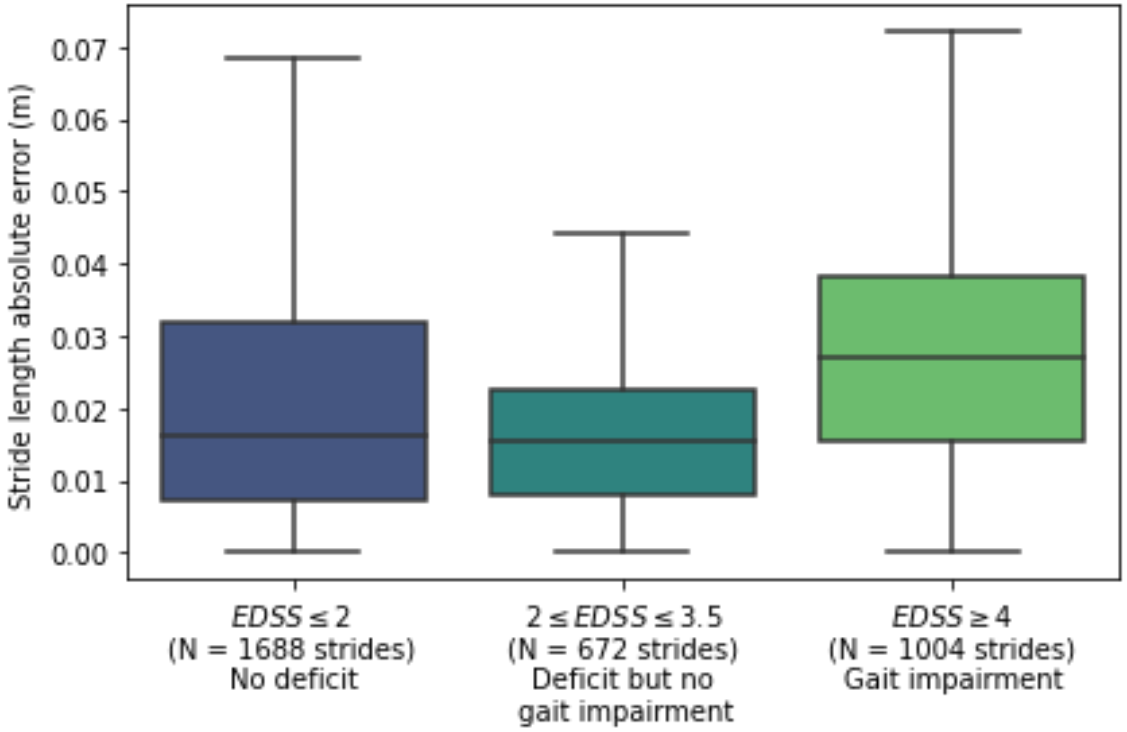


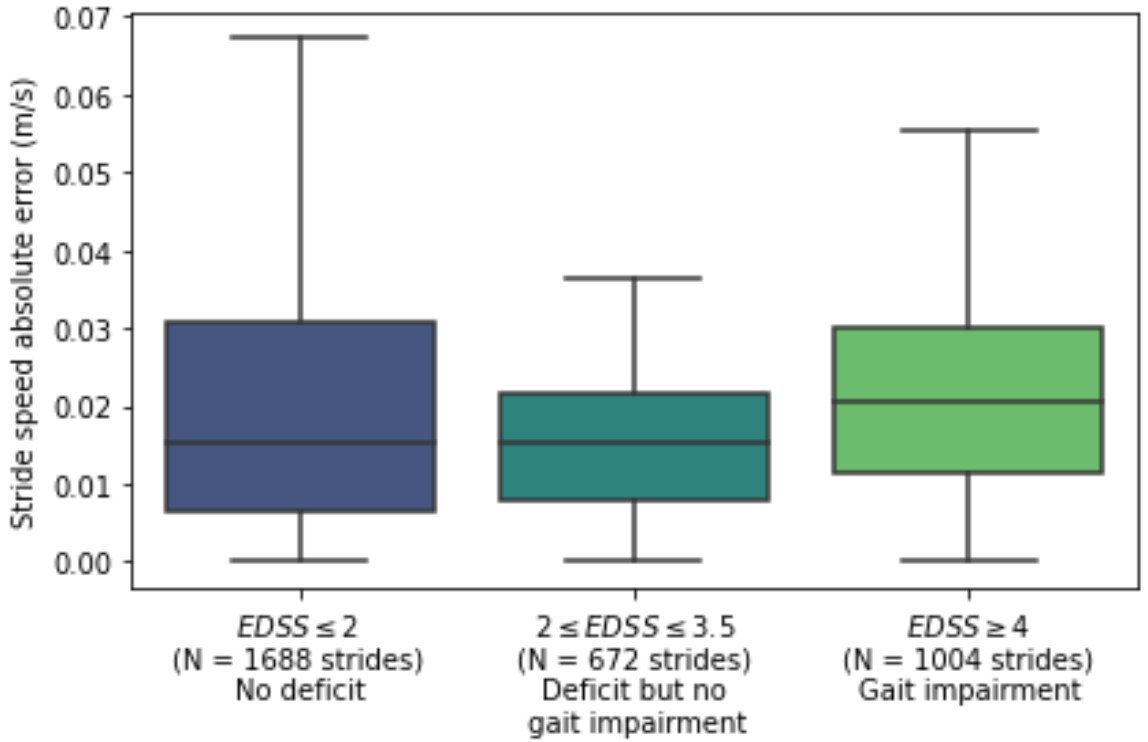
Gait lab (Motion capture set up : 12 cameras, various heights and orientations, total recording space = 7 × 3 m)

exercices:

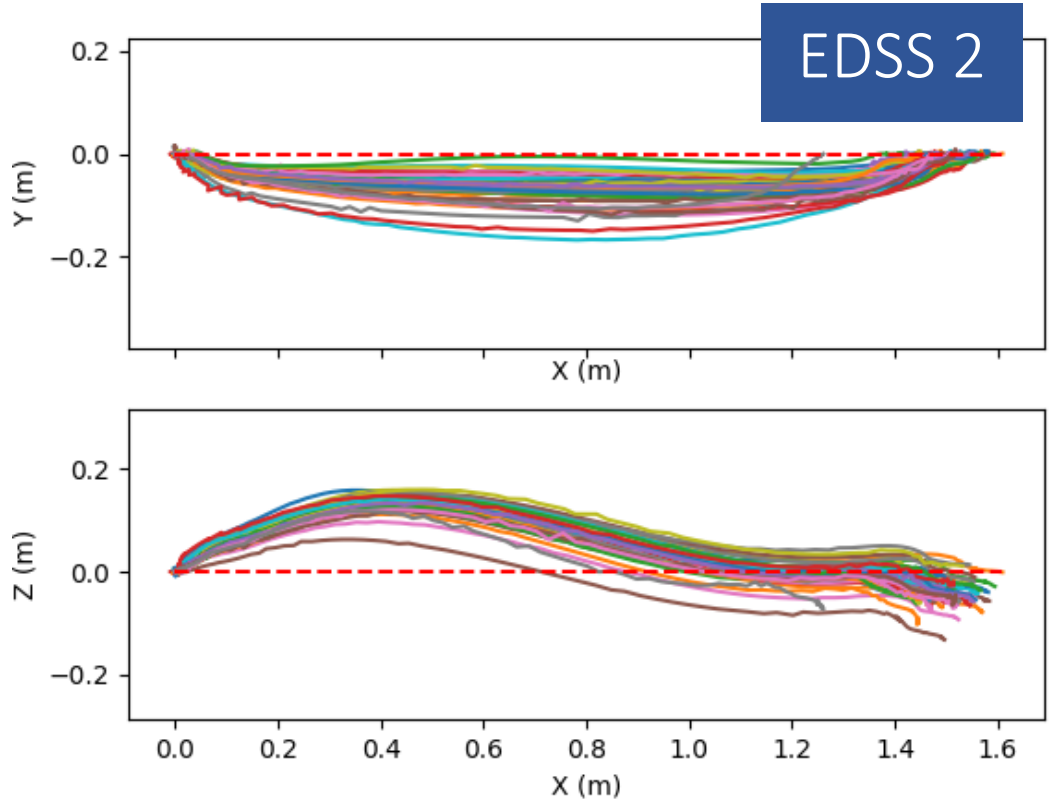
- Confortable 120m walk
- 120m walk with double task (listing unique animals names)
- Fastest 25ft walk (performed twice)
- 3 * 180° turns while walking at a normal pace
- 7m fast walk, 3m normal walk, 7m run

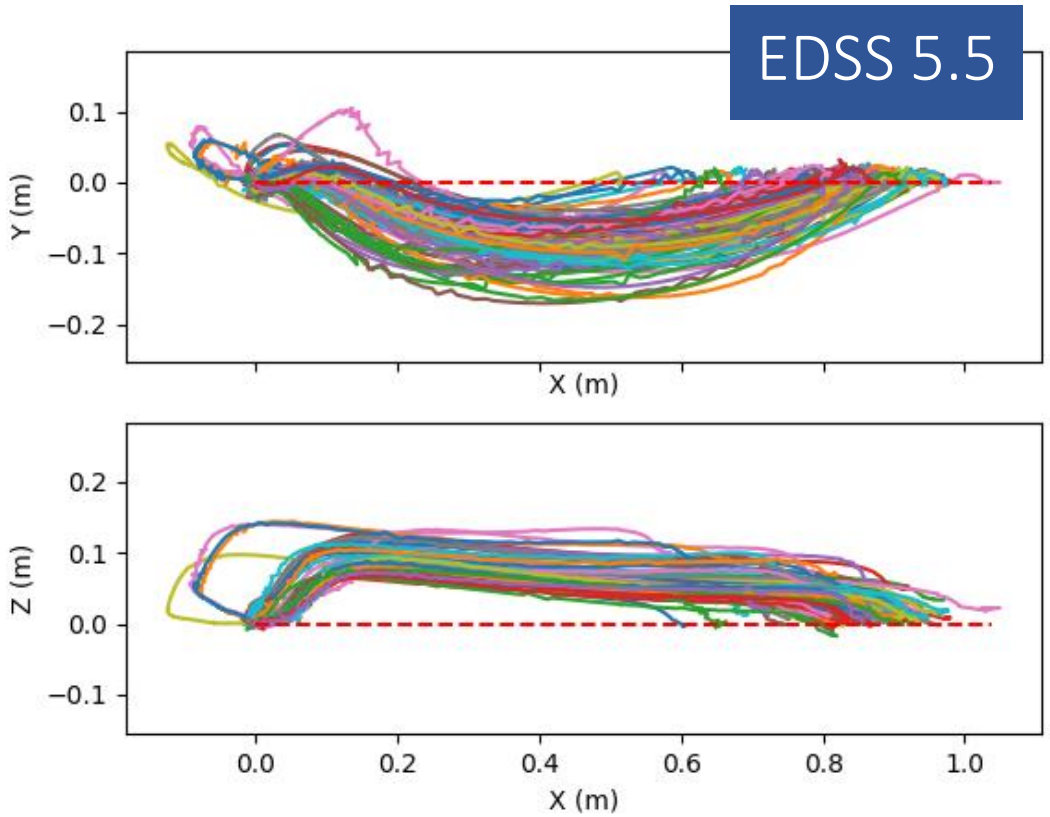
Results

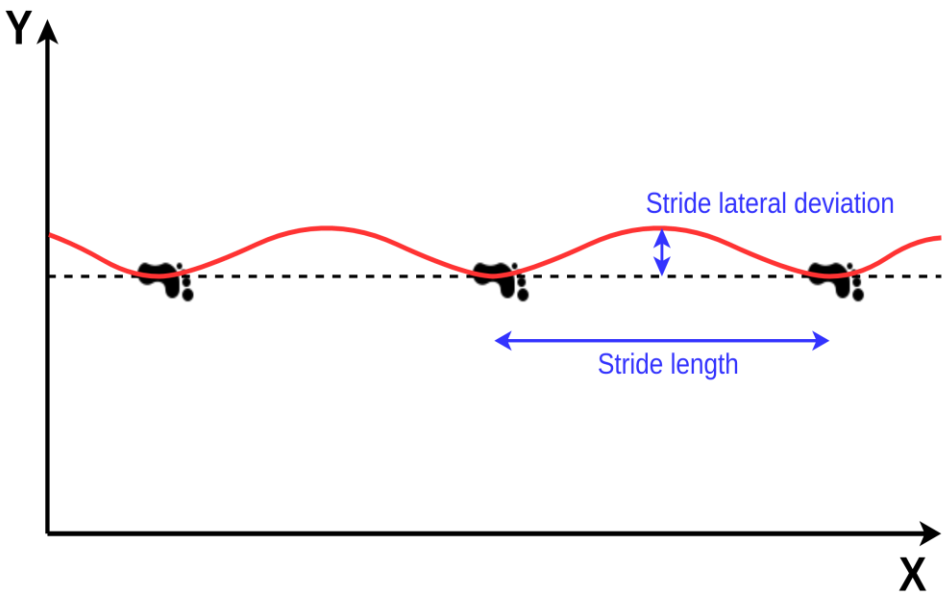


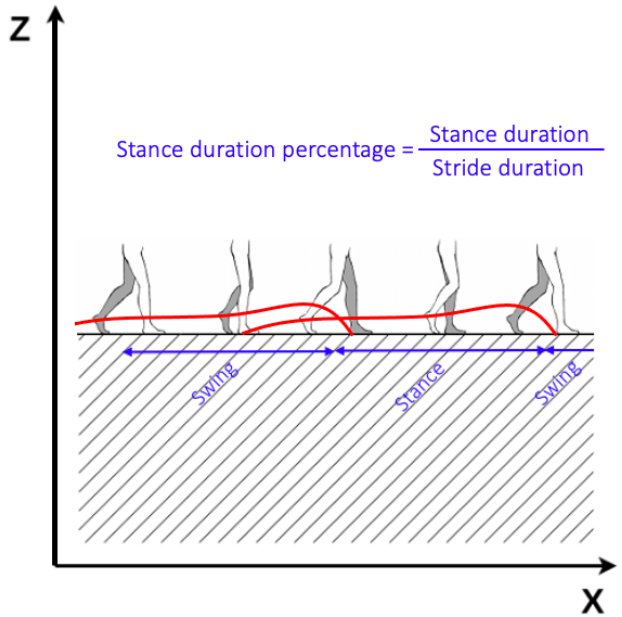


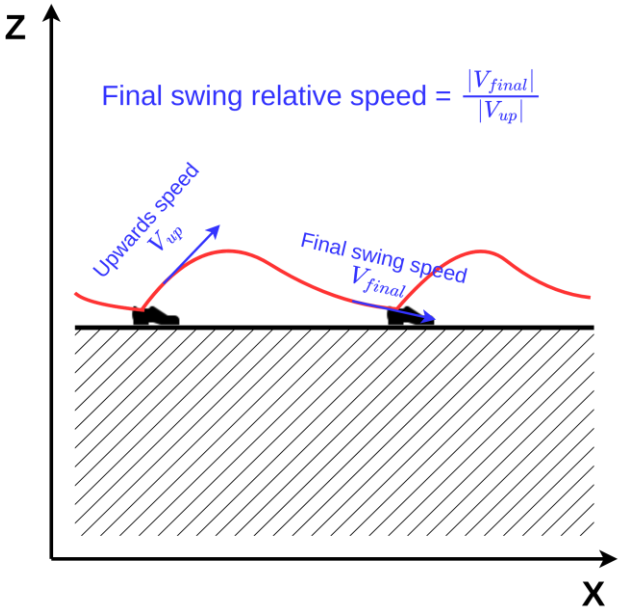
Over 99% of strides identified using the Motion Capture were accurately detected by the IMU device (99% recall), and measured with a centimetric precision (< 3% error on the stride length). There was no significant impact of the level of disability on the error.


EDSS 2
Y (m)
X (m)
Z (m)
X (m)


EDSS 5.5
Y (m)
X (m)
Z (m)
X (m)


Y
Stride lateral deviation
Stride length
X


Z
Stance duration percentage = Stance duration / Stride duration
Swing
Stance
Swing
X


Z
Final swing relative speed = $\frac{|V_{final}|}{|V_{up}|}$
Upwards speed V_{up}
Final swing speed V_{final}
X

ACTIMS: non-controlled environment

Compliance

On 49 recording period, 45 include enough data for analysis : **91% compliance**

19 patients have completed so far the 1 year data

Analytical plan

1. Reliability

2. Validity

3. Longitudinal evolution

1. Reliability

	ICC	SEM	Avg
nb_strides_per_hour	0.93	24	181
distance_per_hour	0.93	23	169
stride_velocity_95	0.99	0.03	1,44
stride length_95	0.99	0.02	1,46
stance_percentage_median	0.97	0.66	64,4
stance_duration_median	0.97	0.03	0,76
walked_distance_90	0.78	13	50,9
swing_duration_median	0.93	0,01	0,42
Benchmark – sv95c on DMD patients from dossier	0.94	0,07	

→ All variables demonstrate a good stability, at the exception of walked distance (90th percentile). Results will be refined with other percentiles in clinical validation phase (e.g., ICC of median is higher)

→ Results include 2 outliers (patients 01-002 and 01-031) with relatively high variability. An analysis with clinicians is ongoing to understand how to interpret this data in the results

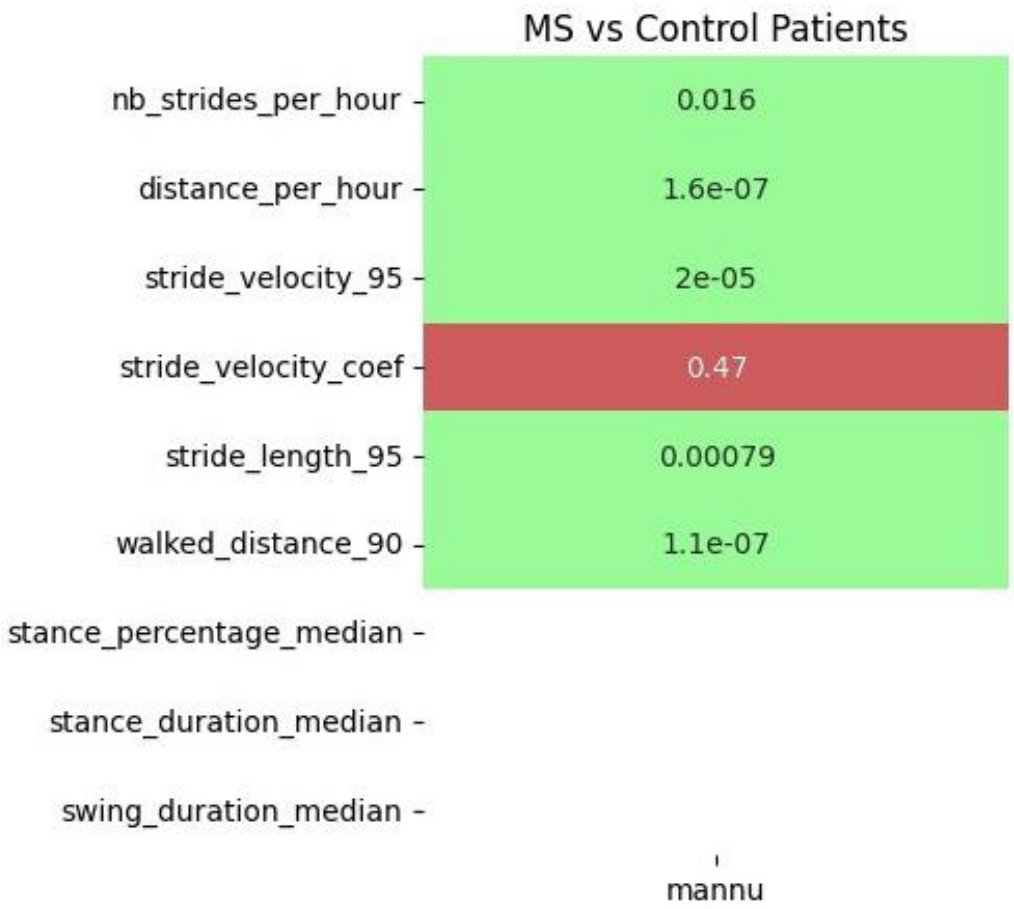
Internal reliability evaluation

ICC : Intra-Class Correlation, computed on two periods formed by the two halves of the first recording period for each patient. Ability to auto-correlate.

SEM : standard error measurement, computed using standard deviation & ICC

2. Discriminant Validity

Mann Whitney test



→ Differences between MS patients & controls are statistically significant

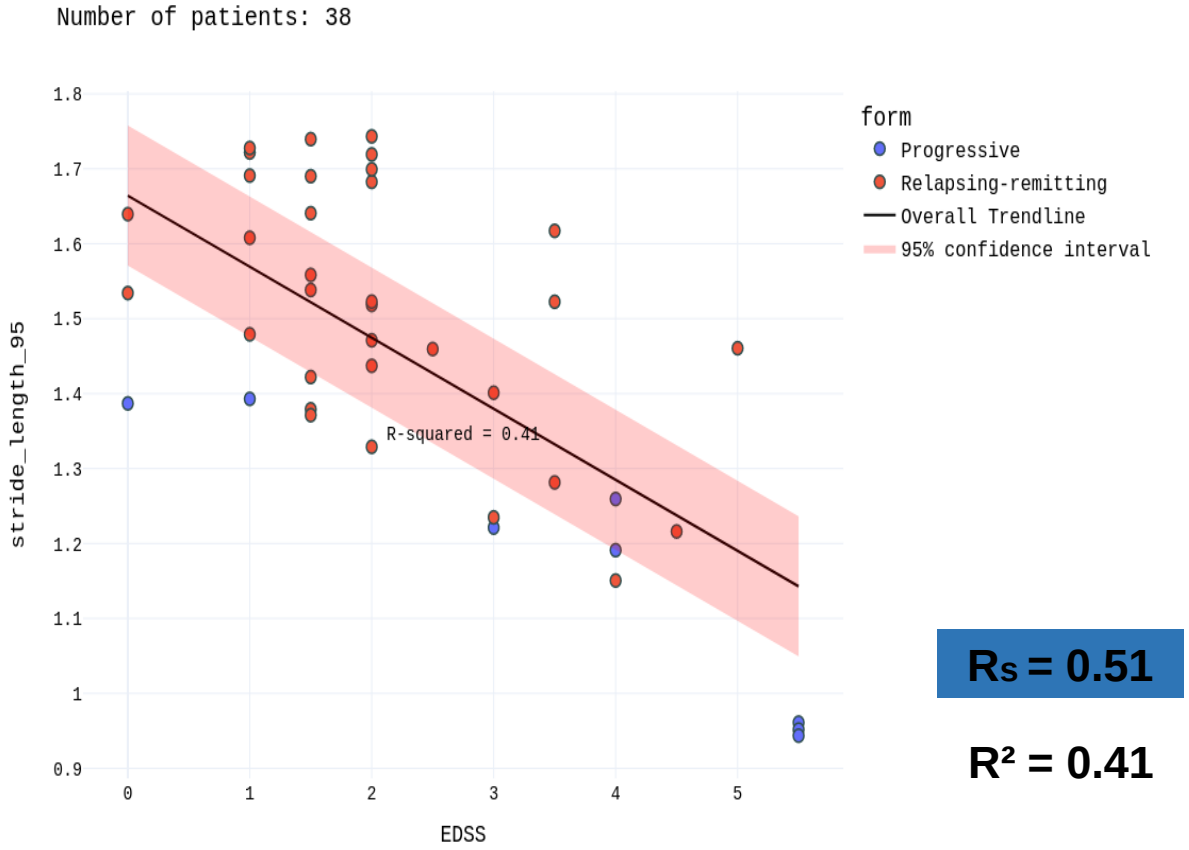
2. Convergent Validity

	Correlation coeff. (Spearman)		
	EDSS	T25FW	6MWT
nb_strides_per_hour	-0.348	-0.45	0.630
distance_per_hour	-0.493	-0.51	0.744
stride_velocity_95	-0.474	-0.62	0.814
stride length_95	-0.510	-0.599	0.731
stance_percentage_median	0.402	0.507	-0.738
stance_duration_median	0.278	0.628	-0.755
walked_distance_90	-0.536	-0.546	0.720
swing_duration_median	-0.176	-0.149	-0.040
Benchmark – sv95c on DMD patients			0.68

p-value <0.01

→ Moderate but significant correlation observed between EDSS/T25FW and SV95C, SL95C & median stance duration

2. Convergent Validity



$R_S = 0.51$

$R^2 = 0.41$

Update article

Wearable inertial sensors provide reliable biomarkers of disease severity in multiple sclerosis: A systematic review and meta-analysis

Aliénor Vienne-Jumeau [a,*], Flavien Quijoux [a,b], Pierre-Paul Vidal [c,a], Damien Ricard [a,d,e]

[a] Cognition and Action Group, Cognac-G, CNRS UMR 8257, Université Paris Descartes, Sorbonne Paris Cité, Service de Santé des Armées, 45, rue des Saints-Pères, 75006 Paris, France
[b] ORPEA Group, 12, rue Jean-Jaurès, CS 10032, 92813 Puteaux cedex, France
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[d] Service de Neurologie de l'Hôpital d'Instruction des Armées de Percy, Service de Santé des Armées, 101, avenue Henri-Barbusse, 92140 Clamart, France
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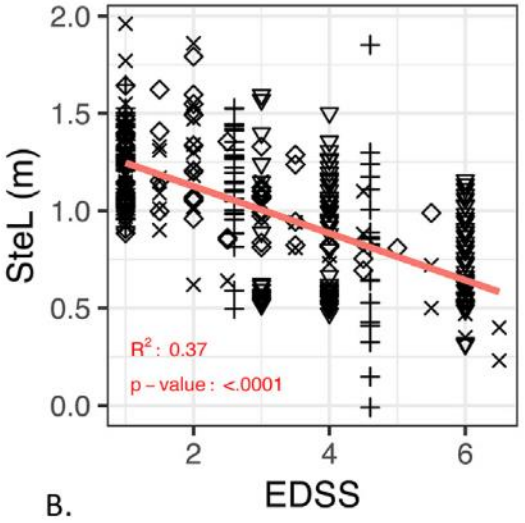
Vienne-Jumeau and al., 2019



Meta analysis of 36 studies, 524 patients

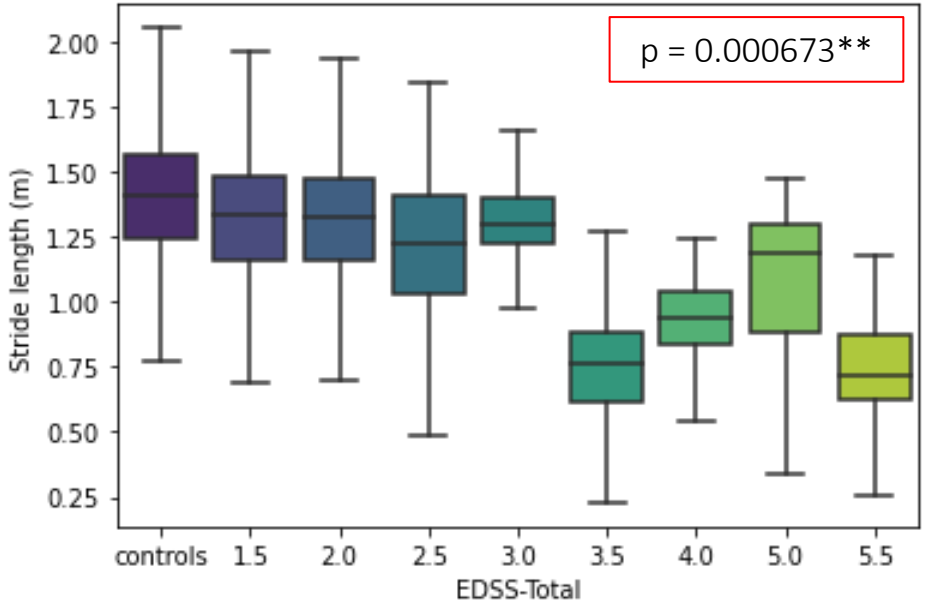
Linear regression line

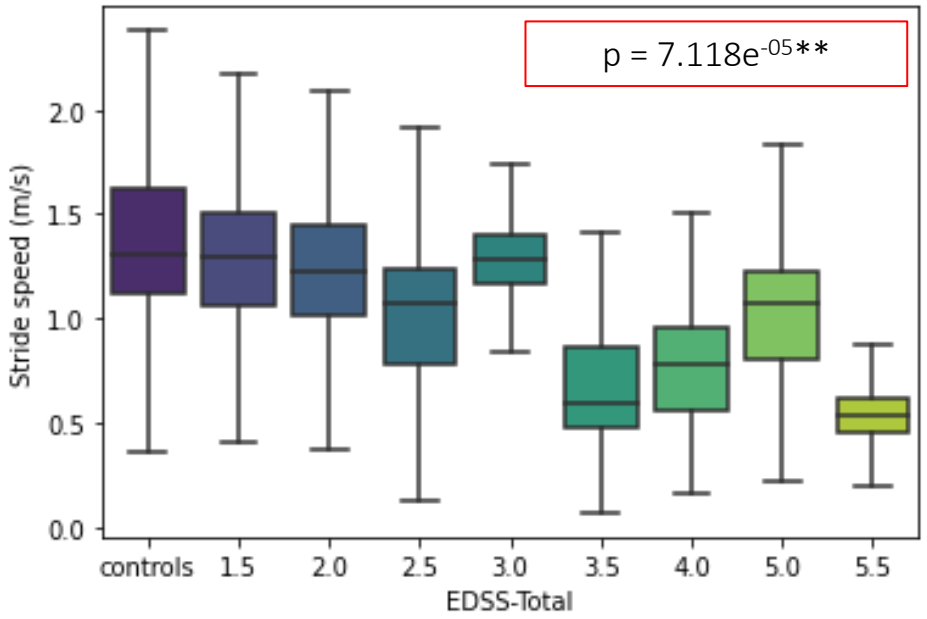
> Correlation of stride length with EDSS consistent with current litterature

STRIDE LENGTH

STRIDE SPEED

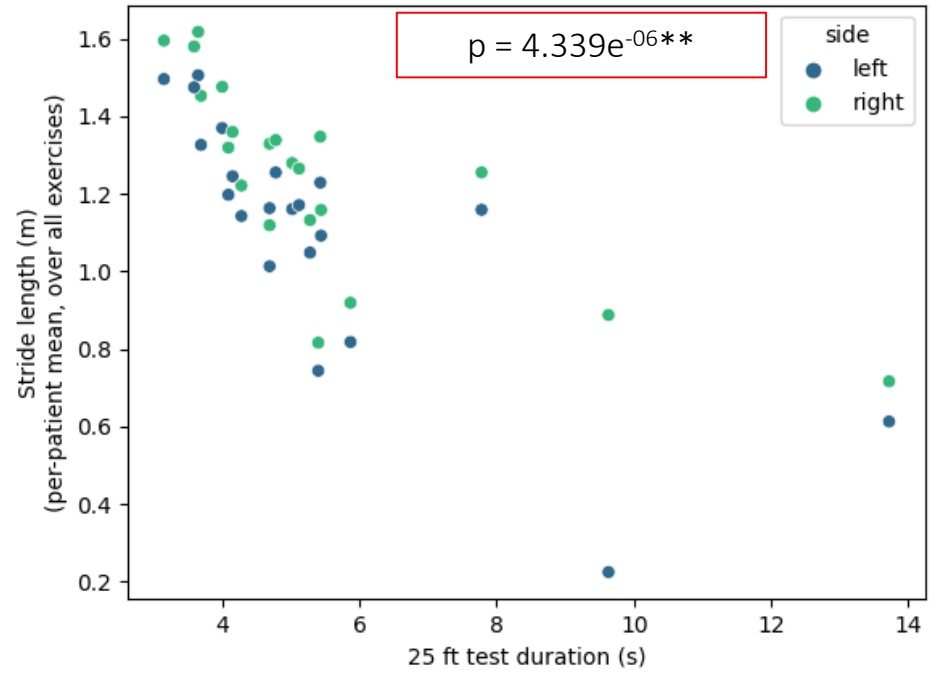
EDSS

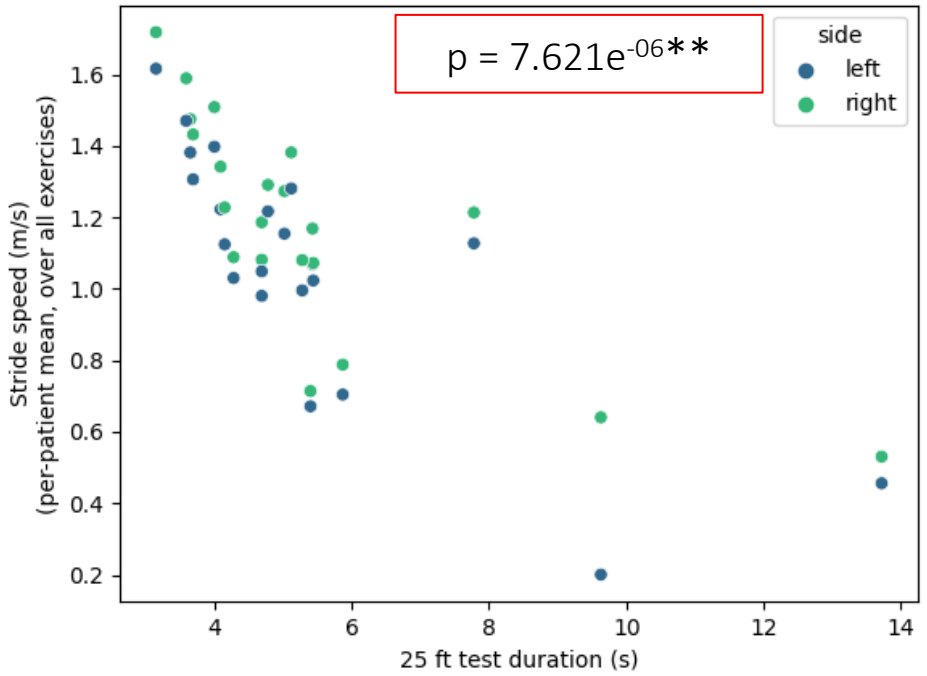




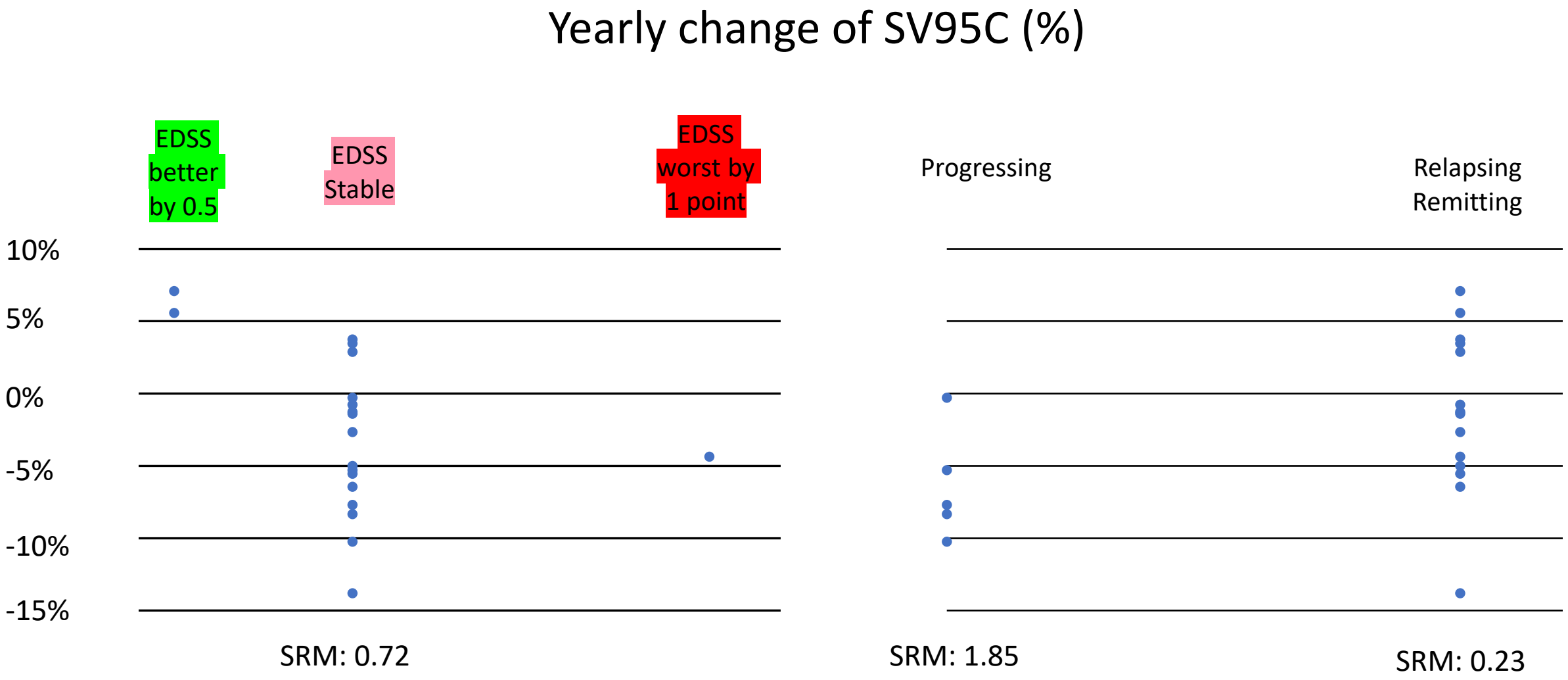
Correlation between digital and gold standard variable (*p<0.05, **p <0.01)

25FTW





3. Sensitivity to change ?



1. Status update on ActiMS study
2. Preliminary results based on existing variables
3. Conclusion & Next steps

Next step

- Patients' follow-up and longitudinal data collection
  - Study extension
- Analysis of the completed baseline and lingitudinal data :
  - Algorithms development and validation
  - Identification of « best outcome … or portfolio of outcome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