syde
By Sysnav Health.

Basel Biometrics Society (BBS) Meeting

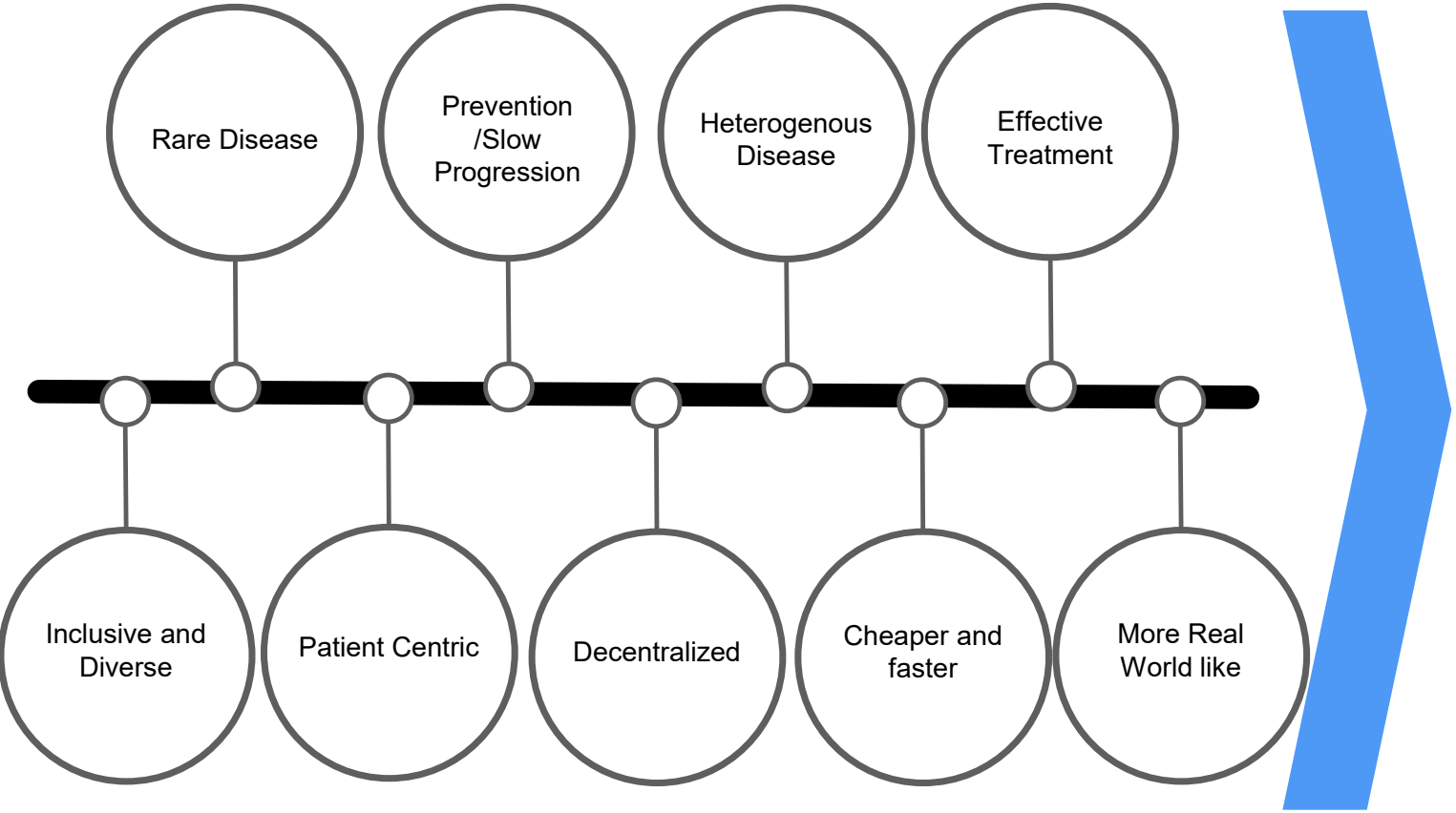
Paul Delmar (Roche)
Damien Eggenspieler (Sysnav)

Basel

06/11/2023

Confidential – do not disclose

A new generation of clinical trials calls for a new generation of endpoints

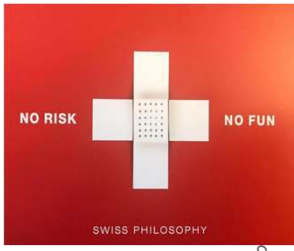


Digital Endpoint

This Photo by Unknown Author is licensed under CC BY-SA-NC

Confidential and proprietary information. Any unauthorized disclosure, distribution or copying is prohibited.

The validation of digital endpoint is a demanding, complex and risky endeavour



- **Regulatory and Professional guidance exist**
  - FDA, DIMEv3, etc…
- **But the pathway for digital endpoint validation needs to be re-invented every time**
- **The bar (level of evidence) is high and requires multi-disciplinary engagement and coordination**

Drug Development

Digital Endpoint Development

Biostatistician :

- Innovation and curiosity
- X-functional Communication
- System Thinking
- Analytical mindset
- Data Science
- Clinical data / Regulated Environment

A complex endpoint validation process needs a rock solid foundation :
Precise and Reliable measurement

Confidential and proprietary information. Any unauthorized disclosure, distribution or copying is pro

The Roche – Sysnav Partnership

- **Roche has formed a strategic partnership with Sysnav for the development of novel endpoint**
- **Match the right technology to the right clinical application**

Sysnav Healthcare announces a multi-year collaboration with Roche.

News 26 JANUARY 2023

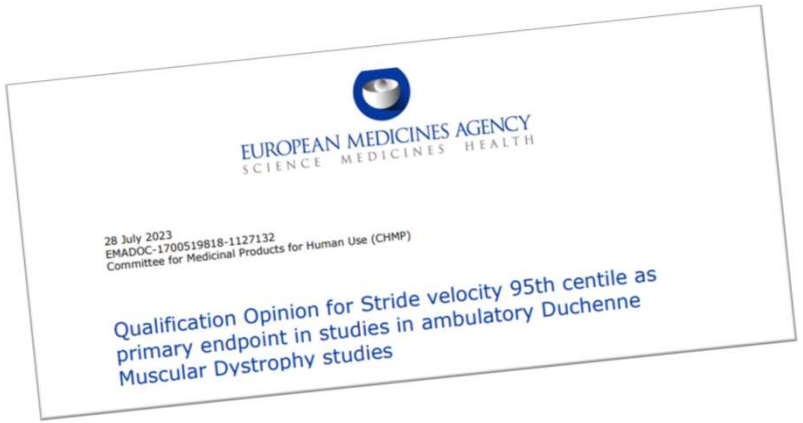
Multi-Year

Roche x sysnav HEALTH CARE

Collaboration

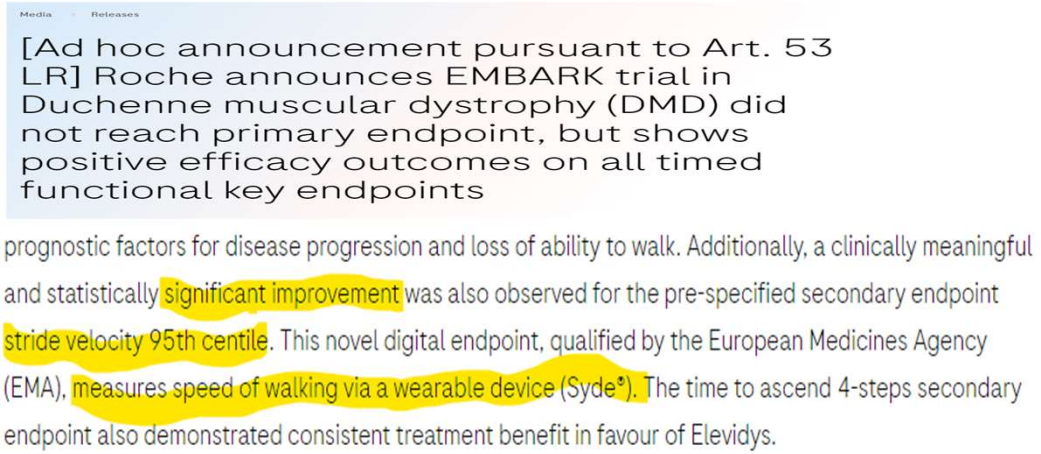
Sysnav Healthcare is pleased to announce a partnership with Roche to facilitate development of industry standard outcome measurements in diseases associated with movement impairments, and to design the next generation of wearable technology.

With potential to impact the advancement of groundbreaking therapies and improve clinical care, we look forward to our continued collaboration with Roche, as we remain united in our mission to unlock innovation and personalised healthcare for patients living with neurological disorders.


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 July 2023
EMADOC-1700519818-1127132
Committee for Medicinal Products for Human Use (CHMP)

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


Media > Releases

[Ad hoc announcement pursuant to Art. 53 LR] Roche announces EMBARK trial in Duchenne muscular dystrophy (DMD) did not reach primary endpoint, but shows positive efficacy outcomes on all timed functional key endpoints

prognostic factors for disease progression and loss of ability to walk. Additionally, a clinically meaningful and statistically significant improvement was also observed for the pre-specified secondary endpoint stride velocity 95th centile. This novel digital endpoint, qualified by the European Medicines Agency (EMA), measures speed of walking via a wearable device (Syde®). The time to ascend 4-steps secondary endpoint also demonstrated consistent treatment benefit in favour of Elevidys.

TO BE CONTINUED,
MANY MORE TO COME …

Confidential and proprietary information. Any unauthorized disclosure, distribution or copying is prohibited.

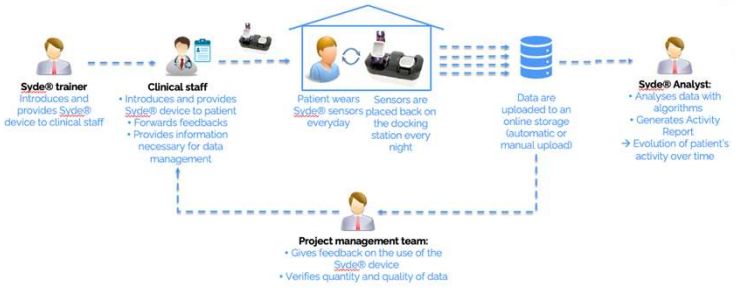
From clinical research to clinical care

- ✓ **Improve treatment decisions** (e.g., start/stop/alter treatment, increase/decrease dose, etc.), especially as more therapies comes on to market or for add-on therapies
- ✓ Enable personalized medicine, by developing attainable **personal targets** & way to continuously monitor it
- ✓ Enabling smarter **payers' schemes**

Before we go any further, a few definition on what is the SV95C

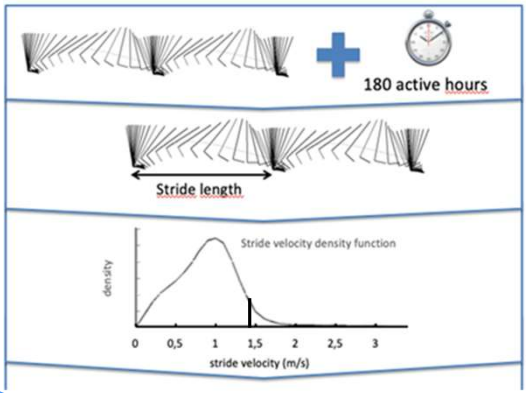
PATIENT PERSPECTIVE:
Passive monitoring measured at the ankle with a suitable wearable device

SV95C



CLINICAL OPERATION PERSPECTIVE:
Defining training strategy, monitoring compliance, ensuring data transfer, …

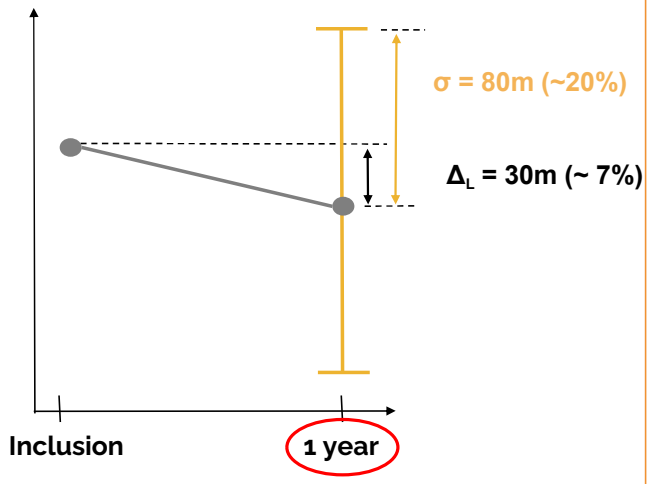
BIOSTAT PERSPECTIVE:
SV95C is an Clinical Outcome Measure, reflective of the top ambulatory performance, meaningful, reliable, and sensitive to change in DMD



Measuring meaningful data

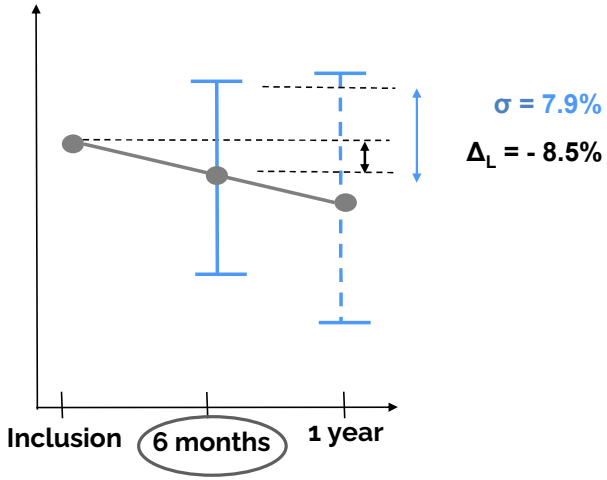
The power of digital endpoint: Number of patients needed in Duchenne Muscular Distrophy to power a trial with 6MWT and SV95C as primary outcome measure

Typical 6MWT in DMD Natural History



6MWT n= 112
@ 1 years

Typical SV95C in DMD Natural History



SV95C N=23
@ 6 months

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

↑ Sensitivity to change
↓ Variability

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

Confidential and proprietary information. Any unauthorized disclosure, distribution or copying is prohibited.

The development requires to develop and validate a number of « sub-systems »

Digital Health Technology (DHT) development

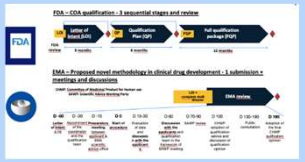
Endpoint development

Endpoint qualification

Device devlpt & verification

Analytical validation

Clinical validation



The device measures angular velocity within 0.02 °/s

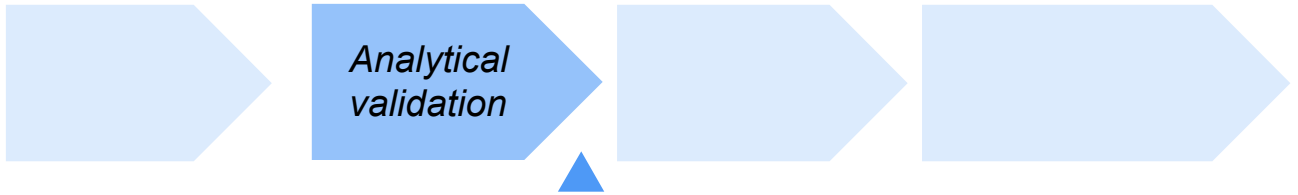
The device measures strides within 3 cm in the CoU

The endpoint measures evolution of disease or drug benefit within 6 months for cohort of N=20

The endpoint is an industry standart

What can go wrong ?

Error 1: Analytical validity everywhere ?



The device measures strides within 3 cm in the CoU

Error 1: The baby bottle experiment

Error 1: Precision of data acquisition system & analytical validity: If you ask the wrong question, you get the wrong answer !

NIH National Library of Medicine
National Center for Biotechnology Information

PMC PubMed Central®

Search PMC Full-Text Archive

Journal List > J Gen Intern Med > v.33(6); 2018 Jun > PMC5975150

Springer | JGIM | Journal of General Internal Medicine
springer.com | This journal | Toc Alerts | Submit Online | Open Choice

J Gen Intern Med. 2018 Jun; 33(6): 795–796.
Published online 2018 Apr 9. doi: 10.1007/s11606-018-4332-y

PMCID: PMC5975150
PMID: 29633143

Tracking Steps on Apple Watch at Different Walking Speeds

Praveen Veerabhadrappa, M.B.B.S., M.S., Ph.D.,[1] Matthew Duffy Moran, B.S.,[1] Mitchell D. Renninger, B.S.,[1] Matthew B. Rhudy, Ph.D.,[2] Scott B. Dreisbach, B.S.,[1] and Kristin M. Gift, B.S.[1]

Author information ▸ Copyright and License information Disclaimer

J Gen Intern Med

Question

How accurate are the step counts obtained from Apple Watch?

Findings

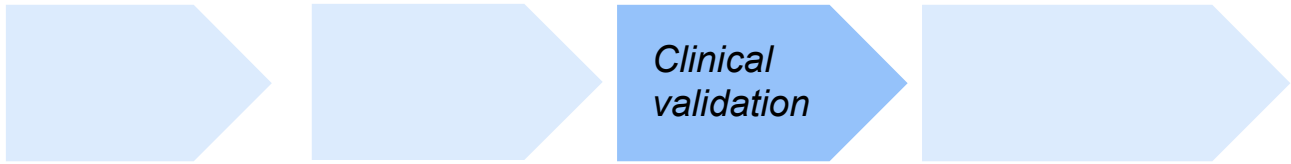
In this validation study, video steps vs. Apple Watch steps (mean ± SD) were 2965 ± 144 vs. 2964 ± 145 steps; $P < 0.001$. Lin's concordance correlation coefficient showed a strong correlation ($r = 0.96$; $P < 0.001$) between the two measurements. There was a total error of 0.034% (1.07 steps) for the Apple Watch steps when compared with the manual counts obtained from video recordings.

Error: 0.034%

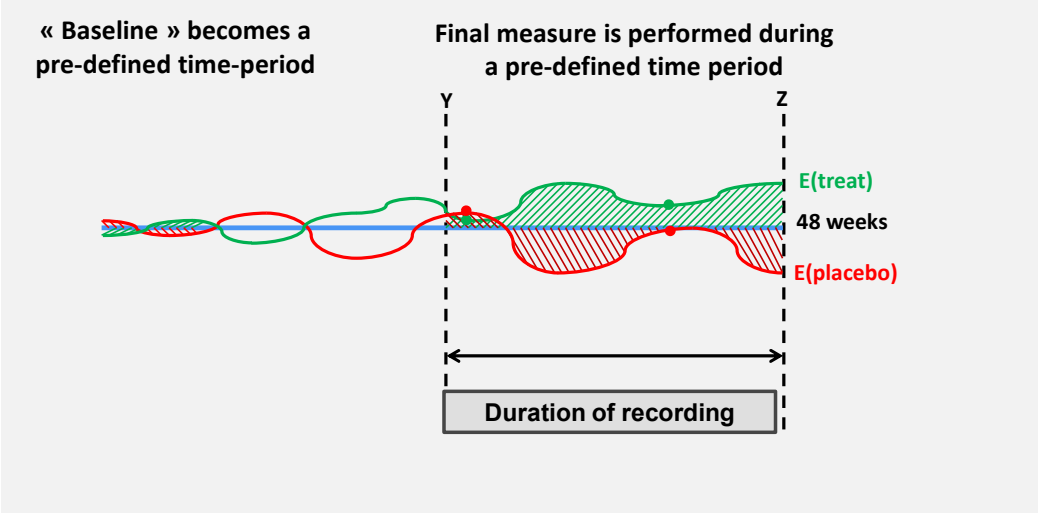
??? context of use ???

Error: 100 %

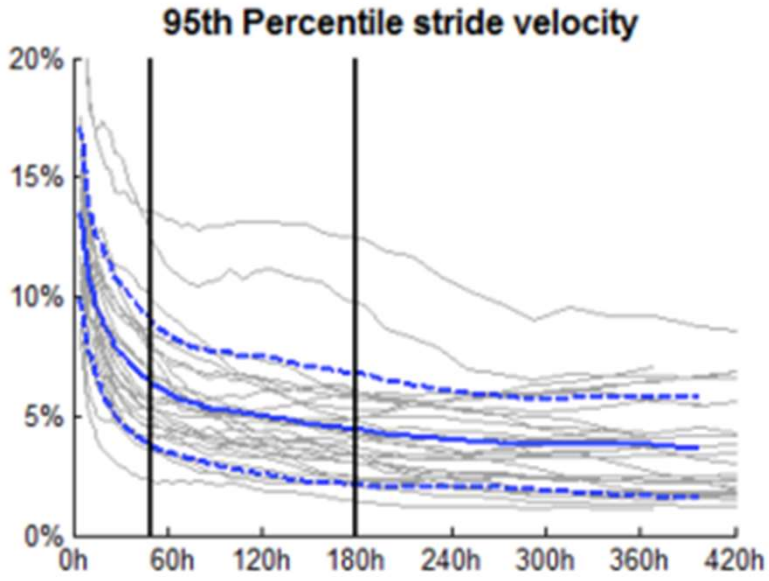
Challenge 2: Defining the endpoint correctly



Challenge 2: Defining duration of recording period required new analytical methods, borrowed to electronics stability



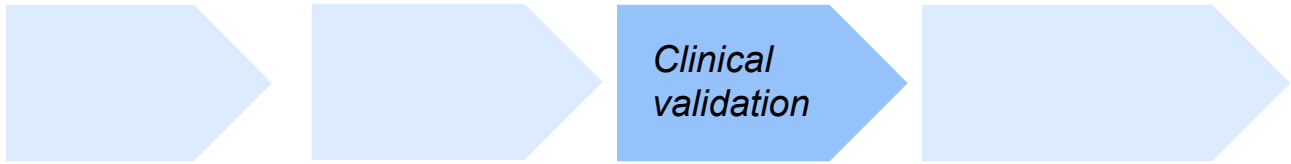
Variability



Duration of recording

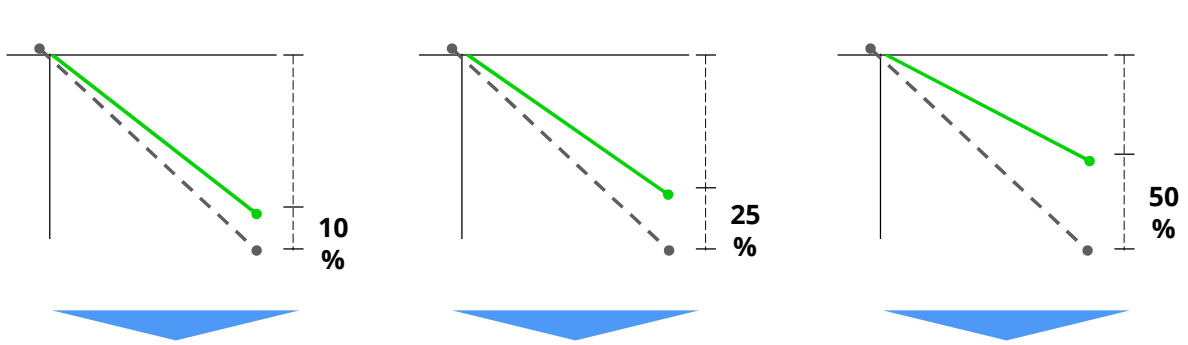
A continuous variable will require to define new variables (like the duration) and new ways to analyze them (eg Allen Variance)

Challenge 3: Not all endpoint are born equal



With the SV95C, we need 10-20 times less ALS patients to power a clinical trial compared to traditional gold standard

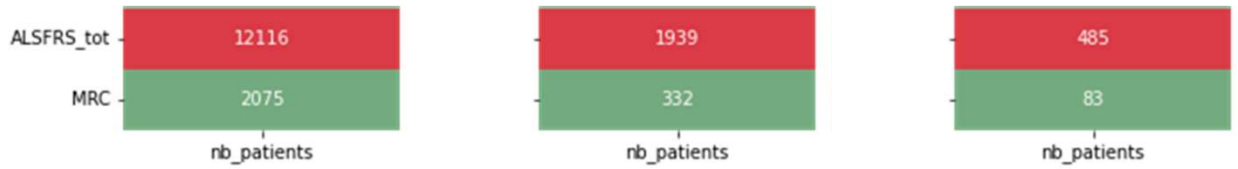
Expected efficacy of compound tested



Number of patients needed in a clinical trial (for a given drug efficacy expected & depending on primary endpoint selected)

Syde variable

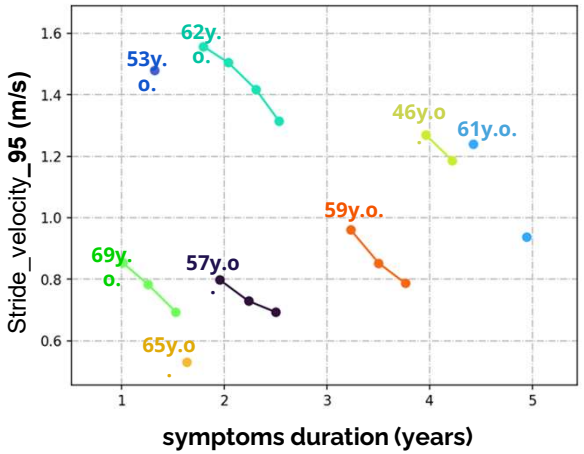
Gold standards

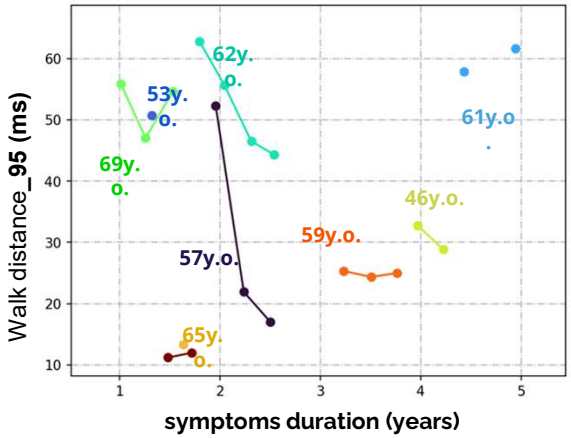


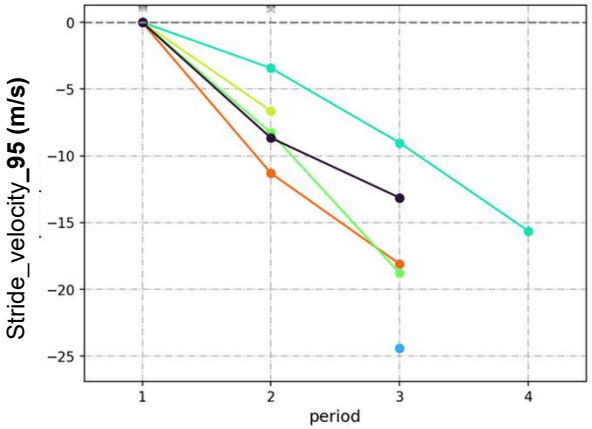
N: 10x

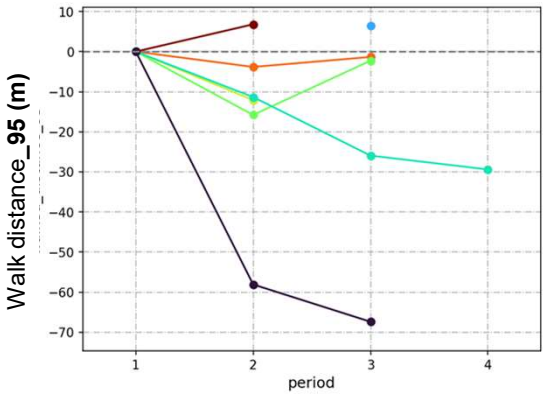
The SV95C is a very robust outcome, because does rely less on motivation & patient environment

Longitudinal evolution of untreated ALS patients measured with SV95C (left, in m/s) and their maximum walking perimeter (right in m)



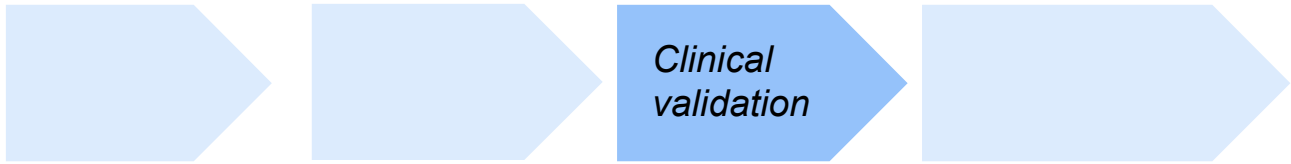






Confidential and proprietary information. Any unauthorized disclosure, distribution or copying is prohibited.

Challenge 3: Not all endpoint are born equal

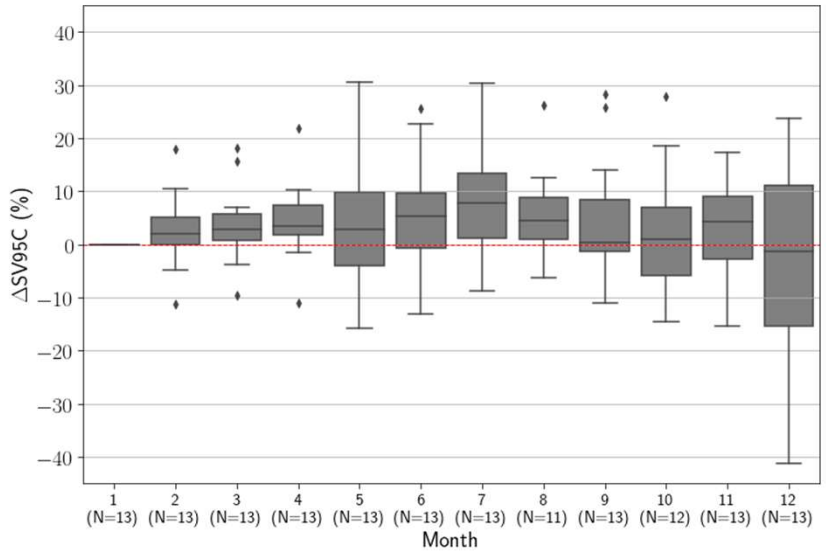


Challenge 4: having robust validation plan, dataset for development & others for validation will help you avoid pitfalls

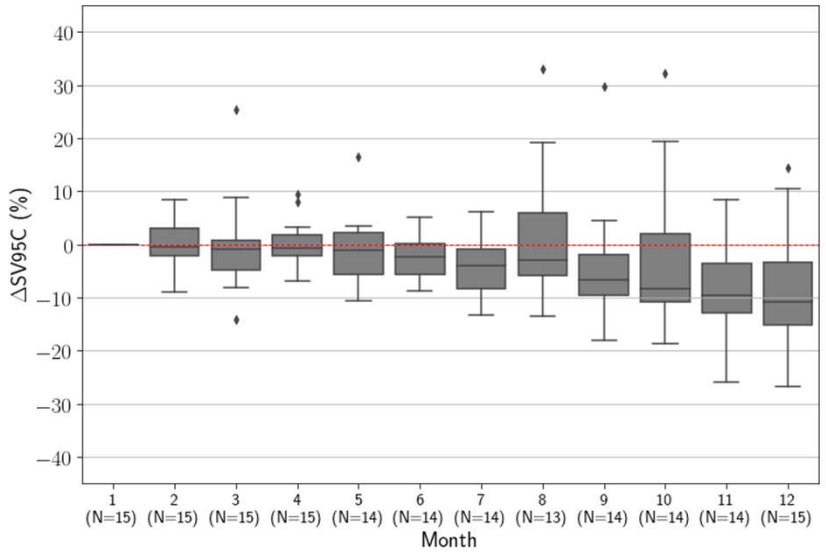
Multi-variate model:
Age, disease progression, patient development, severity, different phenotypes, treatment adaptation, seasonality, treatment response, ….

DMD, a progressive disease ?

Young population [5-7]



Old population [8-14]



We need the right skillset in the room to avoid missing the important verification & validation

Digital biomarkers have the potential to improve clinical research

We need smart biostats to develop new industry standards

Thank you to all the Patients
Funders
Physicians
Collaborators
who participate to this work