

The long and winding road of digital outcome: From academic study to regulatory qualification

Prof. Laurent Servais, Oxford University



Conflict of interest

Laurent Servais has given consultancy in the digital field to Roche-Sysnav-Aparito-Dyne and Biogen

LS hold a patent on a method to estimate energy expenditure at the upper limb level with no financial return



digital outcome

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Save

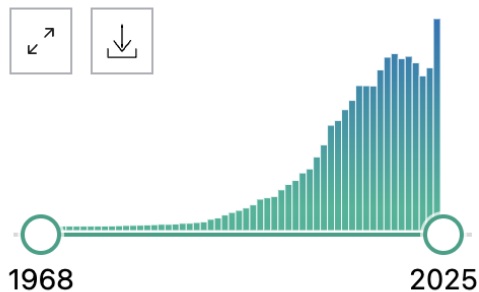
Email

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MY CUSTOM FILTERS 

132,063 results

RESULTS BY YEAR



1

Cite

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TransCatheter aortic percutaneous coronary replacement and cor valve stenosis and c international, multic controlled trial.

Kedhi E, Hermanides RS, Amat-Santos IJ, Andreas



outcome measures wearable device

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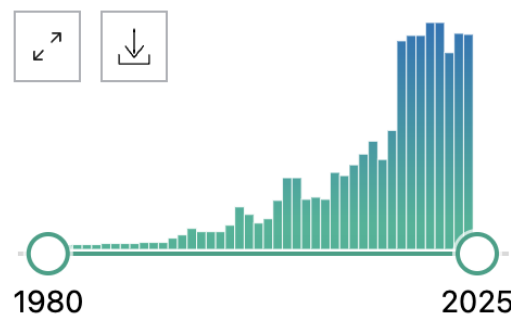
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2,335 results

RESULTS BY YEAR



1

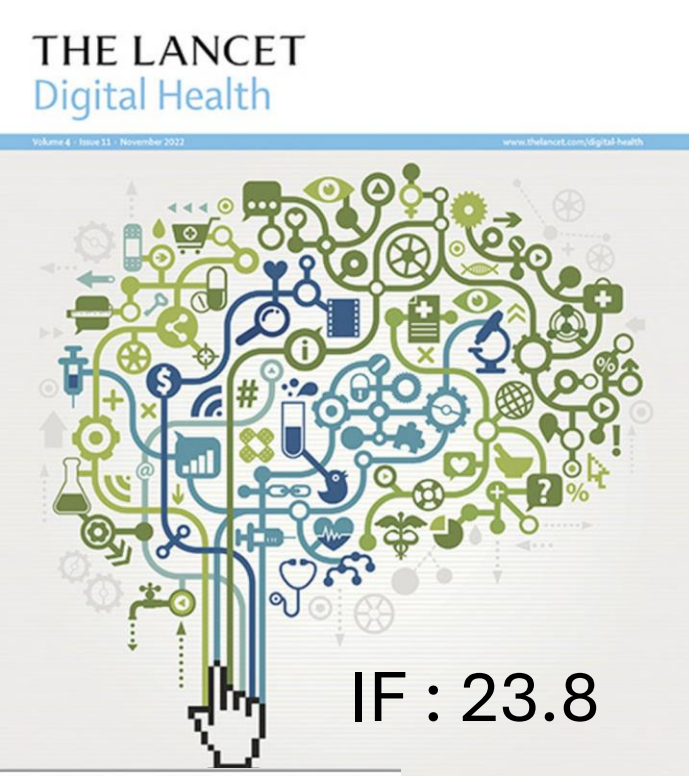
Cite

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Patient Preferences in Cochle

Freeman MH, Patro A, Lindquist NR, Moberly AC, Haynes DS, Bennett MI
Otol Neurotol. 2025 Jan 1;46(1):54-
PMID: 39627903

INTERVENTIONS: Survey administer
Sources of information regarding CI
deciding on a manufacturer, and ma



npj | Digital Medicine

IF : 15.35

OPEN ACCESS

Digital Health

8 | 1 | 24

Digital Biomarkers

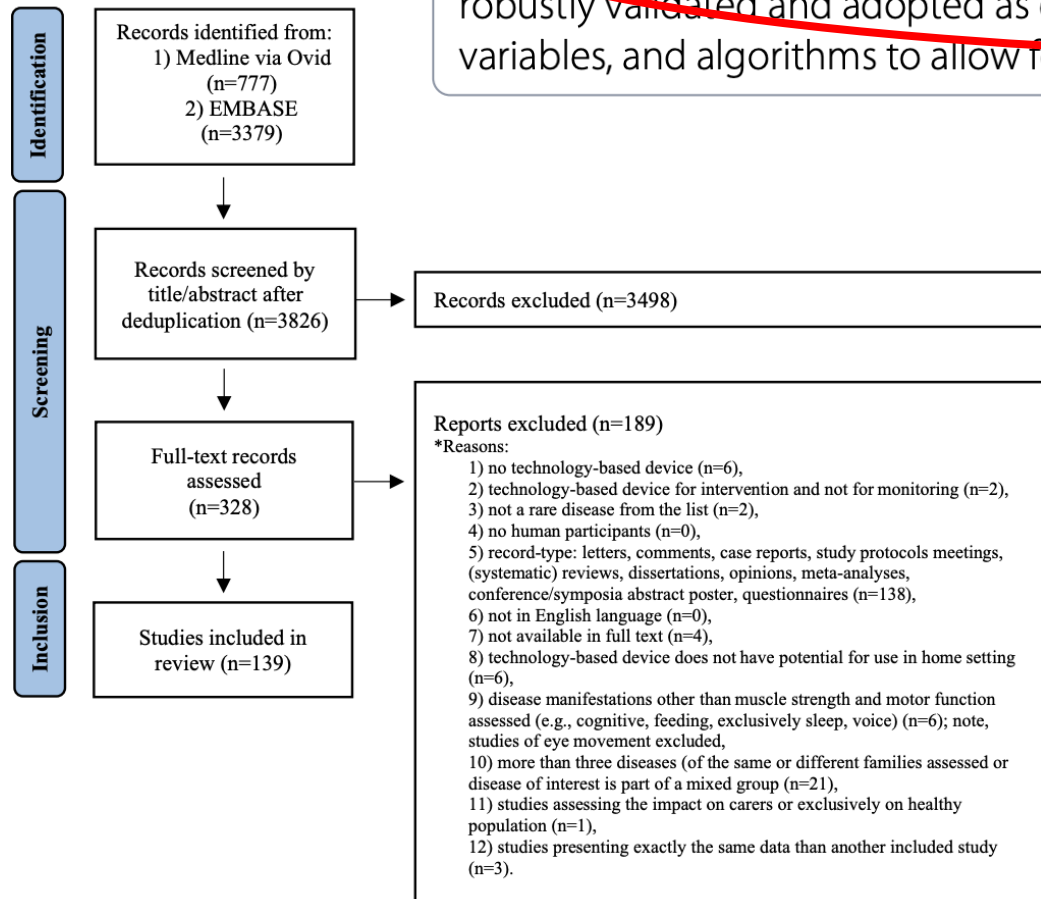


PLOS Digital Health



Abstract

Developing drugs for rare diseases is challenging, and the precision and objectivity of outcome measures is critical to this process. In recent years, a number of technologies have increasingly been used for remote monitoring of patient health. We report a systematic literature review that aims to summarize the current state of progress with regard to the use of digital outcome measures for real-life motor function assessment of patients with rare neurological diseases. Our search of published literature identified 3826 records, of which 139 were included across 27 different diseases. This review shows that use of digital outcome measures for motor function outside a clinical setting is feasible and employed in a broad range of diseases, although we found few outcome measures that have been robustly validated and adopted as endpoints in clinical trials. Future research should focus on validation of devices, variables, and algorithms to allow for regulatory qualification and widespread adoption.



Poleur *et al.*
Orphanet Journal of Rare Diseases (2023) 18:224
<https://doi.org/10.1186/s13023-023-02813-3>

Orphanet Journal of
Rare Diseases

REVIEW

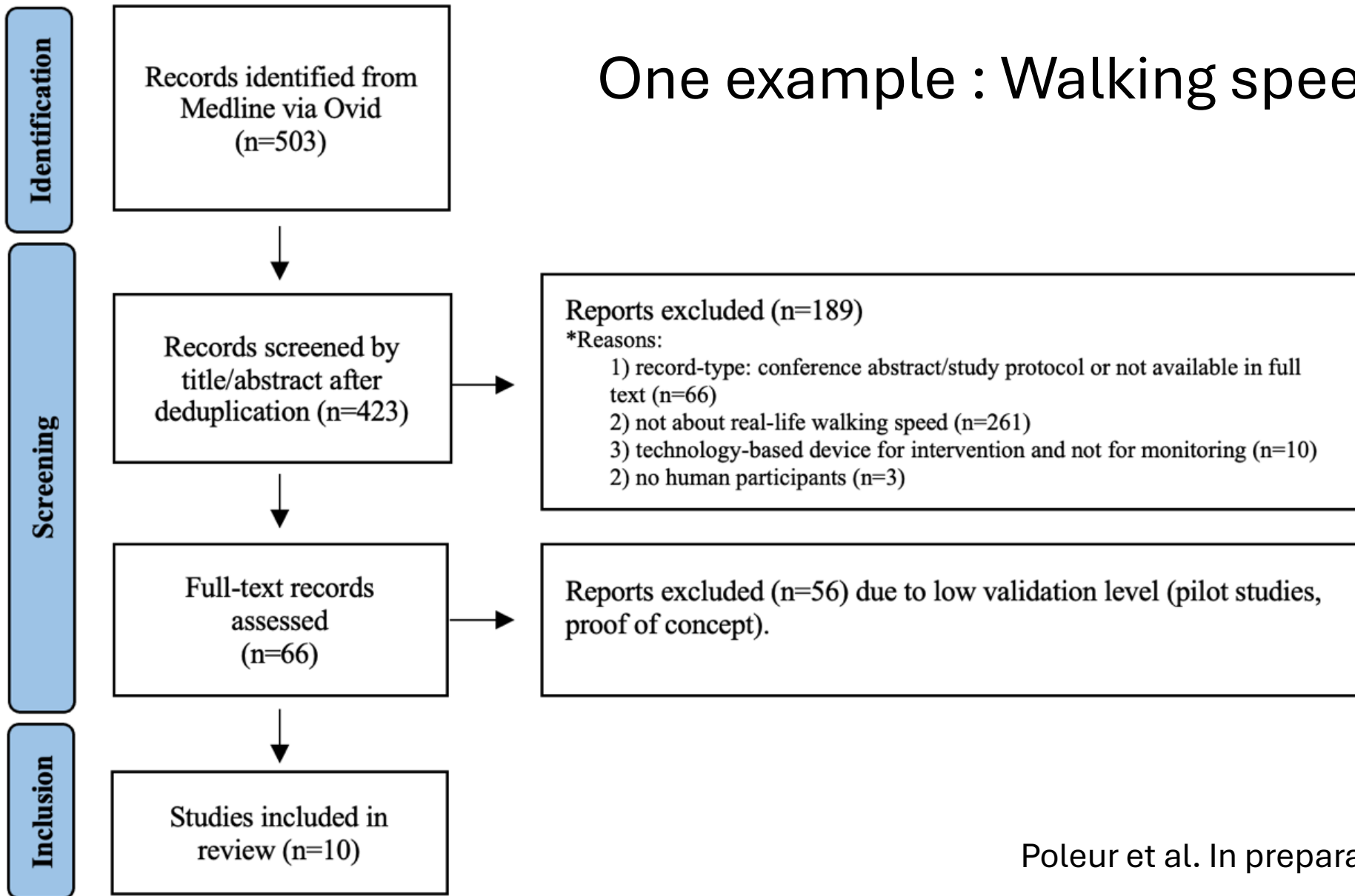
Open Access

The use of digital outcome measures in clinical trials in rare neurological diseases: a systematic literature review

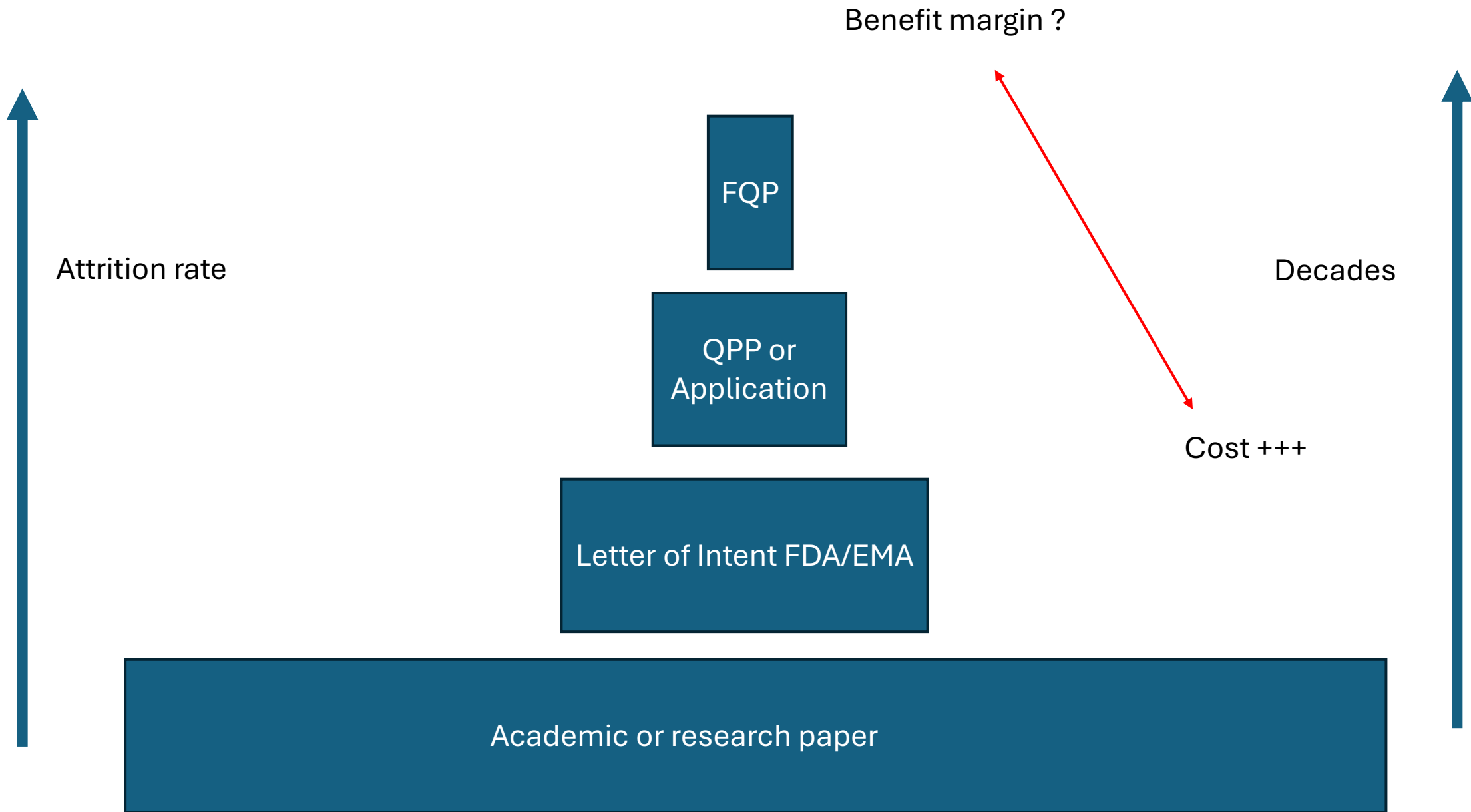
Margaux Poleur^{1,3,4*}, Theodora Markati² and Laurent Servais^{2,3}



One example : Walking speed

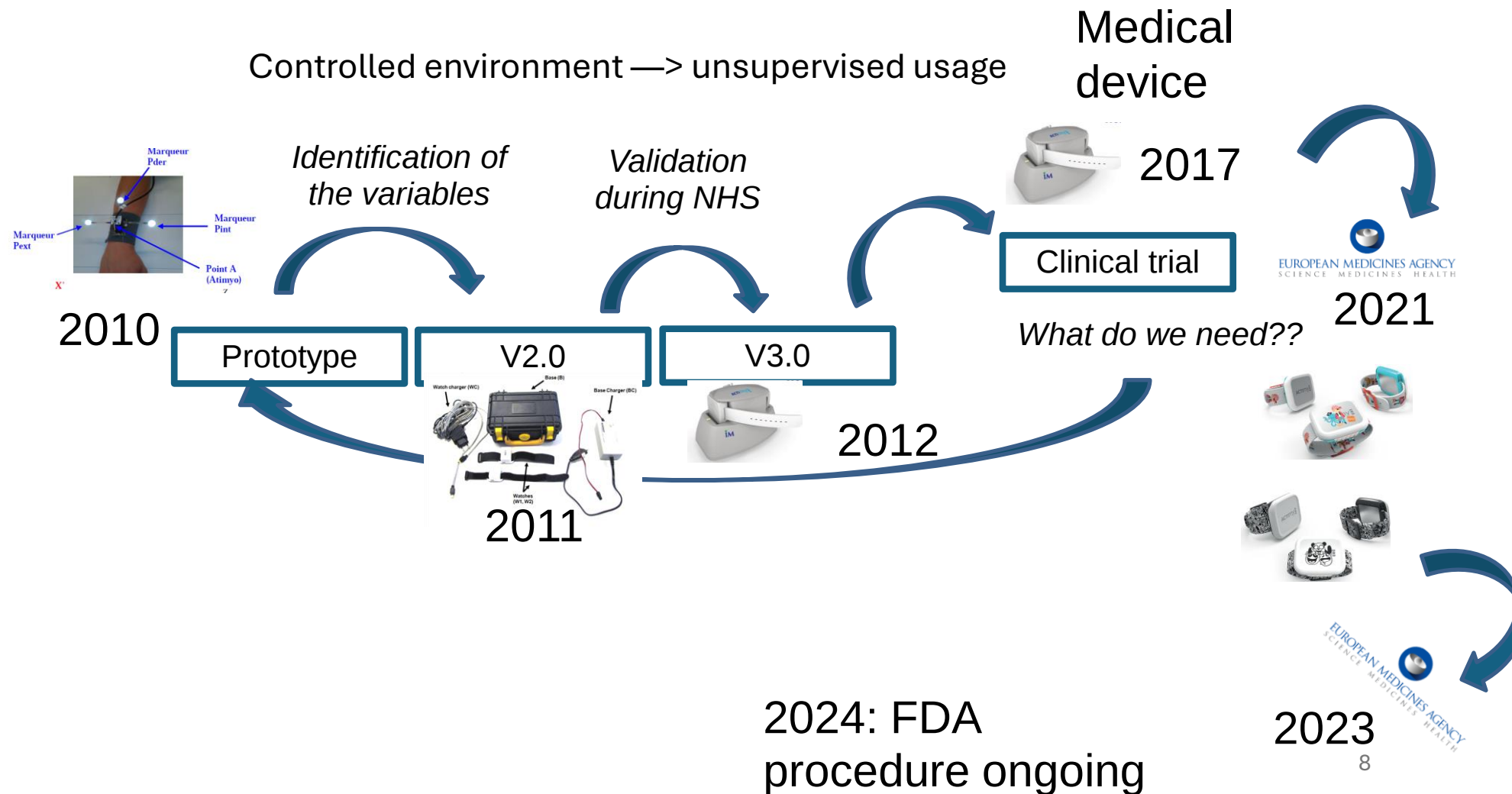


Poleur et al. In preparation



The long and winding road of SV95C

Technical development timeline



What is SV95C?

Stride velocity 95th centile (SV95C) :
a measure of top ambulatory speed of a patient in real life

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Correspondence | [Published: 09 October 2023](#)

First regulatory qualification of a digital primary endpoint to measure treatment efficacy in DMD

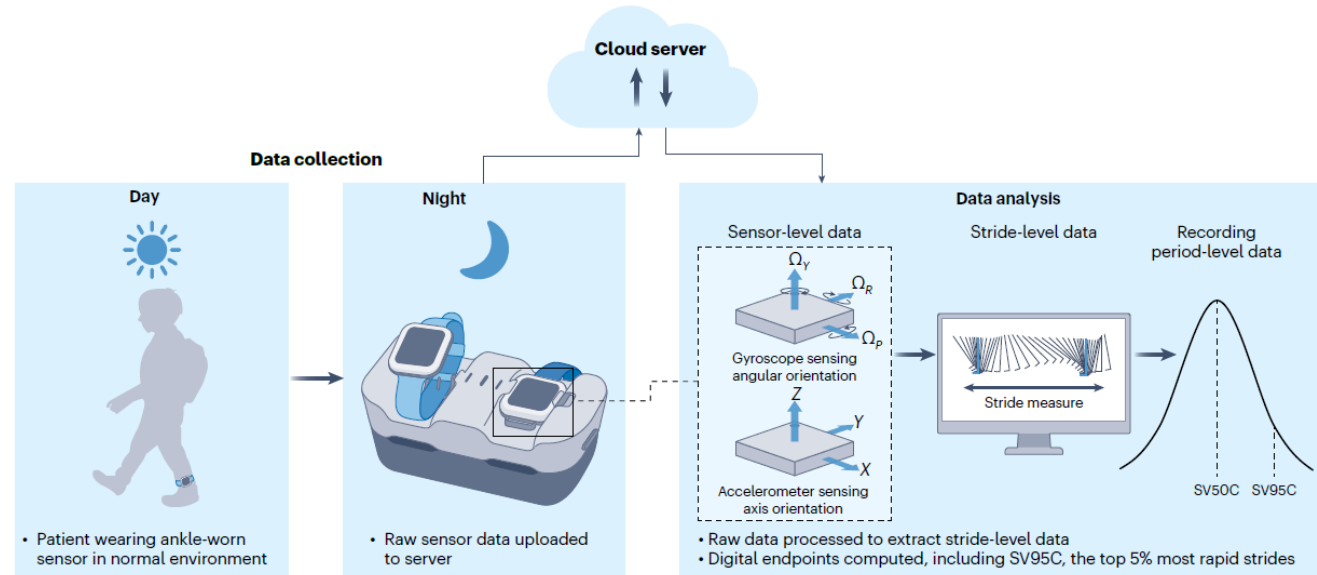
[Laurent Servais](#) , [Damien Eggenspieler](#), [Margaux Poleur](#), [Marc Grelet](#), [Francesco Muntoni](#), [Paul Strijbos](#) & [Mélanie Anoussamy](#)

[Nature Medicine](#) **29**, 2391–2392 (2023) | [Cite this article](#)

992 Accesses | 2 Citations | 2 Altmetric | [Metrics](#)

Above 4 y/o

Servais L, *et al.* Nat Med. 2023;29(10):2391-2392.



Continuous data collection in the real-world setting with 2 **wearable inertial sensors** (on each ankle)

www.nature.com/scientificreports

scientific reports

OPEN

Evidentiary basis of the first regulatory qualification of a digital primary efficacy endpoint

[Laurent Servais](#)^{1,2,3}, [Paul Strijbos](#)³, [Margaux Poleur](#)⁴, [Andrada Mirea](#)^{5,6}, [Nina Butoianu](#)⁷, [Valeria A. Sansone](#)⁸, [Carole Vuillerot](#)⁹, [Ulrike Schara-Schmidt](#)¹⁰, [Mariacristina Scoto](#)¹¹, [Andreea M. Seferian](#)¹², [Stefano C. Previtali](#)¹³, [Már Tulinus](#)¹⁴, [Andrés Nascimento](#)^{15,16}, [Pat Furlong](#)¹⁷, [Teji Singh](#)¹⁸, [Roxana Donisa Dreghici](#)¹⁹, [Nathalie Goemans](#)²⁰, [Eugenio Mercuri](#)^{21,22}, [Volker Straub](#)²³, [Maitea Guridi Ormazabal](#)²⁴, [Jessica Braid](#)²⁴, [Francesco Muntoni](#)¹¹, [Alexis Tricot](#)²⁵, [Mélanie Anoussamy](#)²⁵ & [Damien Eggenspieler](#)²⁵

Key questions asked by regulators

Device

- ✓ Medical device
- ✓ CE-labelled
- ✓ Sensors properties
- ✓ Sensors calibration
- ✓ Usability
- ✓ Compliance
- ✓ **Data integrity**

Outcome

- ✓ Qualitative study
- ✓ Context of use
- ✓ Clinical validity
- ✓ Analytical validity
- ✓ External validity
- ✓ Reliability
- ✓ Recording period
- ✓ ((variability))-interference
- ✓ **MCID**
- ✓ **Sensitivity to positive change**
- ✓ Sensitivity to negative change
- ✓ Normative values
- ✓ Discrimination between groups

Height and Death

The measure is very reliable (ICC of 0.99999)

The measure is very sensitive to change SRM $\gg 1$
(especially between 0 and 18 years)

You can easily demonstrate that people with height < 100 cm have a 15 years longer life expectancy than people > 170 cm

You can easily measure MCID with an anchor based method

You can easily show that height is inversely correlated with the most frequent causes of death (Heart infarction- stroke-cancer-suicide...)

So- Height qualifies as a good surrogate outcome for death- and could be used as a primary endpoint for a drug that stops growth in a subgroup of patients (0-15 years) who are unlikely to reach the primary endpoint within a year....

In several conditions (Duchenne- dermatomyositis)- drug that stop the increase of height delay the age at death...



Key opportunities for clinical development

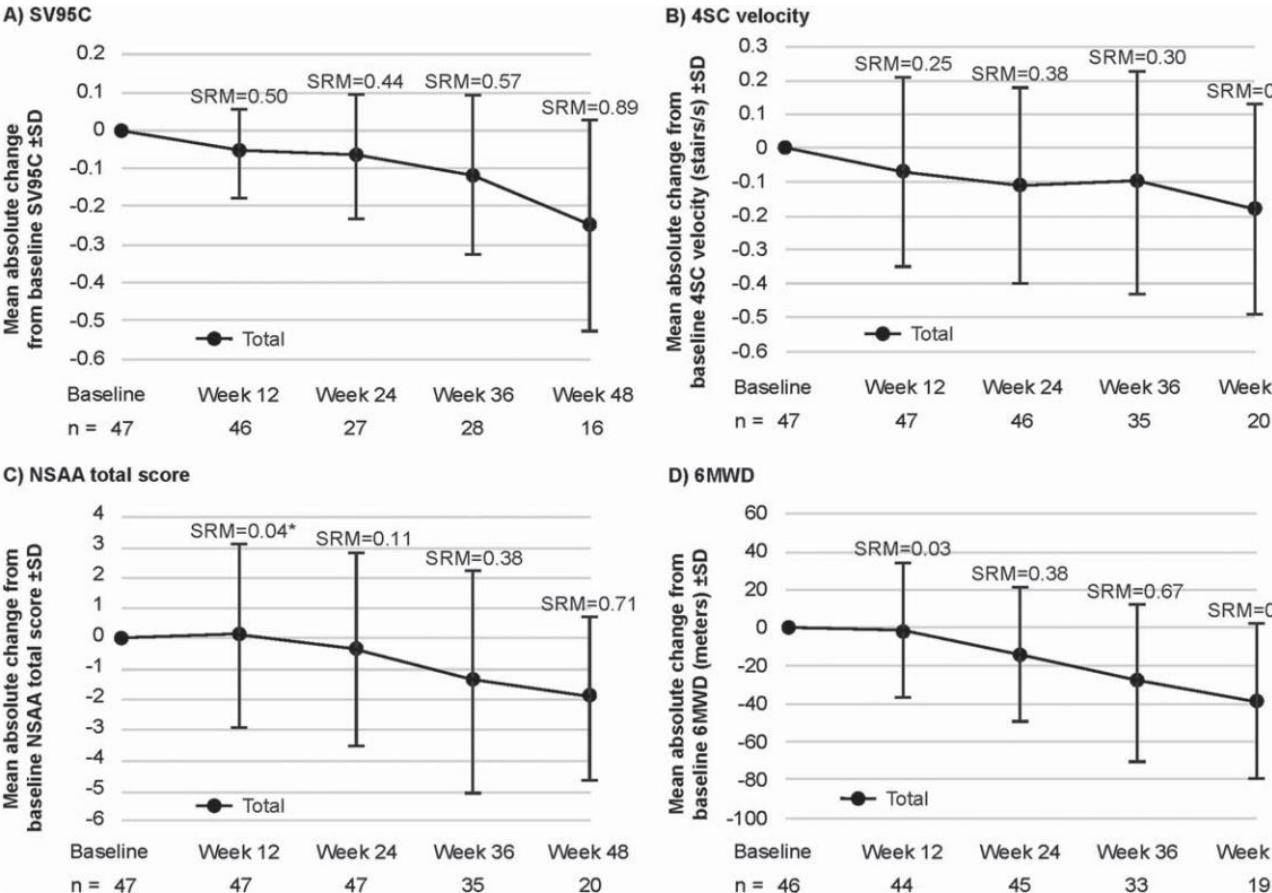
1. Early detection of decline

Journal of Neuromuscular Diseases 11 (2024) 701–714
DOI 10.3233/JND-230188
IOS Press

Research Report

Stride Velocity 95th Centile Detects Decline in Ambulatory Function Over Shorter Intervals than the 6-Minute Walk Test or North Star Ambulatory Assessment in Duchenne Muscular Dystrophy

Michael Rabbia^a, Maitea Guridi Ormazabal^b, Hannah Staunton^c, Klaas Veenstra^b, Damien Eggenspieler^d, Mélanie Annoussamy^d, Laurent Servais^{e,f} and Paul Strijbos^{b,*}

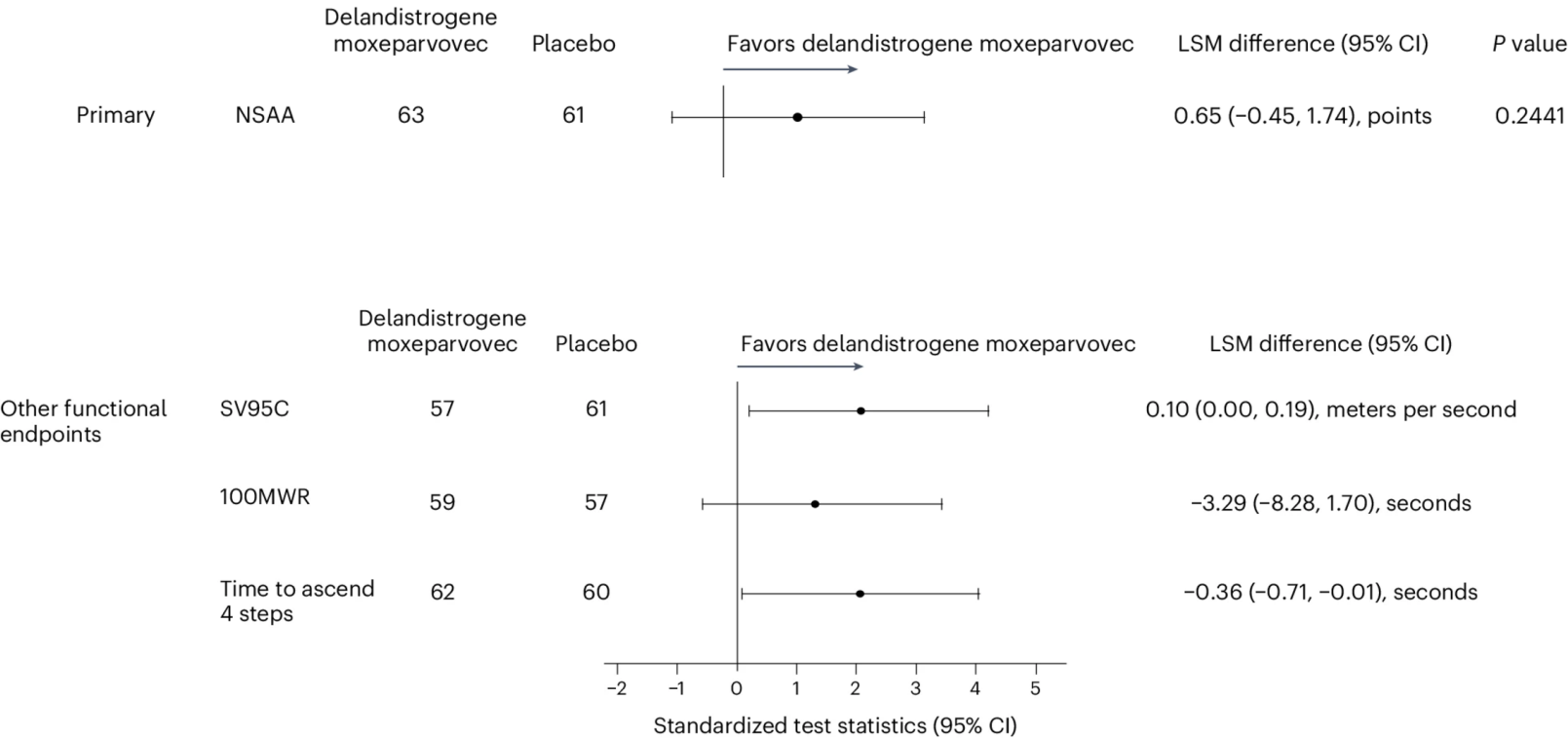


AAV gene therapy for Duchenne muscular dystrophy: the EMBARK phase 3 randomized trial

[Jerry R. Mendell](#) , [Francesco Muntoni](#), [Craig M. McDonald](#), [Eugenio M. Mercuri](#), [Emma Ciafaloni](#), [Hiroyuki Komaki](#), [Carmen Leon-Astudillo](#), [Andrés Nascimento](#), [Crystal Proud](#), [Ulrike Schara-Schmidt](#), [Aravindhan Veerapandiyar](#), [Craig M. Zaidman](#), [Maitea Guridi](#), [Alexander P. Murphy](#), [Carol Reid](#), [Christoph Wandel](#), [Damon R. Asher](#), [Eddie Darton](#), [Stefanie Mason](#), [Rachael A. Potter](#), [Teji Singh](#), [Wenfei Zhang](#), [Paulo Fontoura](#), [Jacob S. Elkins](#) & [Louise R. Rodino-Klapac](#)

[Nature Medicine](#) (2024) | [Cite this article](#)

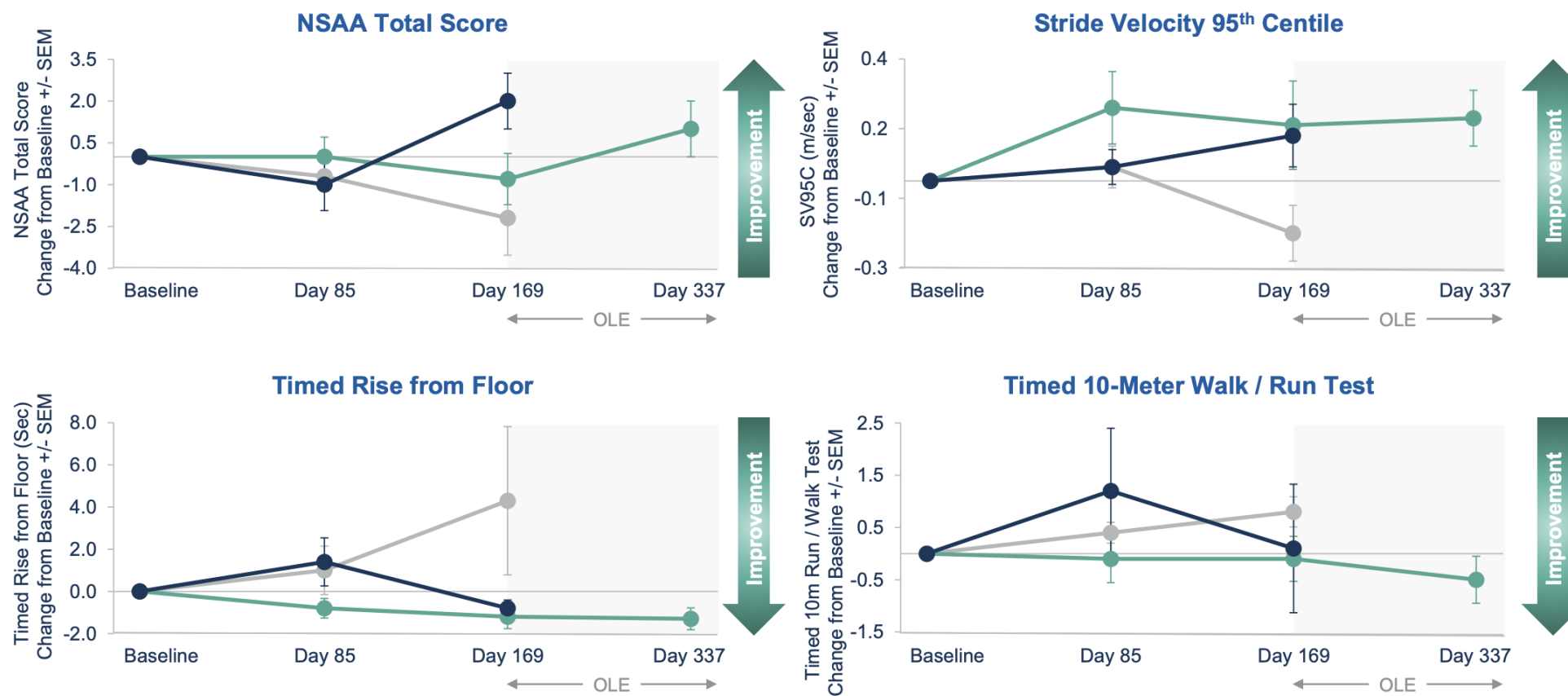
2. Avoid the risk of false negative



3. Early detection of clinical benefit

Improvements Across Multiple Functional Endpoints in Multiple Cohorts

Baseline Values Inform Interpretation of Data; Ongoing Exploration of Longer Timepoints



● Placebo (n=6 for SV95C and n=14 for other endpoints) ● DYNE-251 10 mg/kg Q4W (n = 6 for all endpoints)¹ ● DYNE-251 20 mg/kg Q4W (n = 6 for all endpoints)

1. During the OLE, all participants in 10 mg/kg cohort were dose escalated to 20 mg/kg Q4W regimen.

4. Application in other conditions like Multiple Sclerosis

Adherence

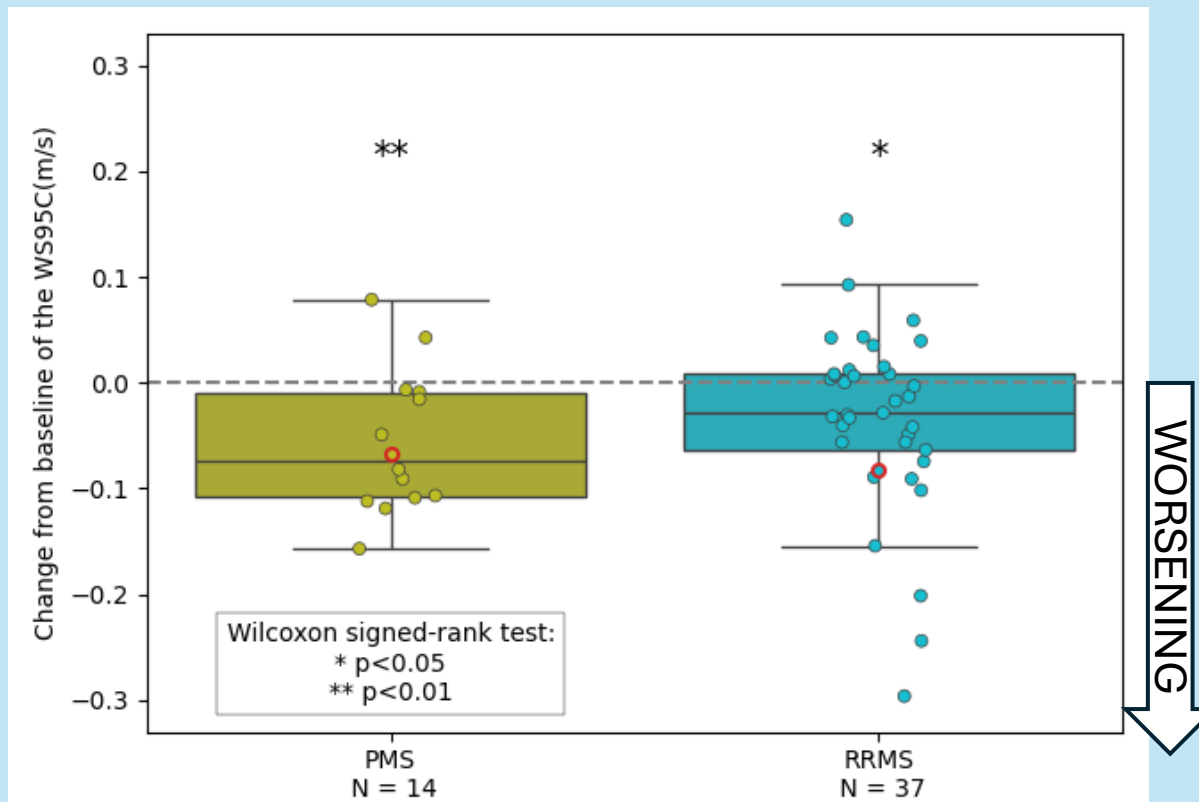
Reliability

Known-group validity

Convergent validity

Ability to detect change

Walking Speed 95th centile



• Participants who experienced relapse(s) between visits

5. The challenge of measuring ambulatory function in very young patients



Ask him to do something and hope that he does exactly what you want...



It would be best to not ask him anything and let him do what HE wants...

Baseline characteristics of all subjects

population	N	median age (sd) (y/o)	age range (y/o)
Patient	28	2.98 (1.0)	1.34 - 4.95
Control	35	2.72 (1.05)	1.07 - 4.86

Excellent compliance with DHT wear

Number and percentage of subjects with more than 50 and 180 hours of data recorded on each ankle sensor

population	N	< 50h	50h ≤ ... < 180h	≥ 180h
Patient	28	1 (3 %)	4 (14 %)	23 (83 %)
Control	35	0 (0 %)	4 (11 %)	31 (89 %)

> 95% patients provide ≥ 50h of recordings with the DHT

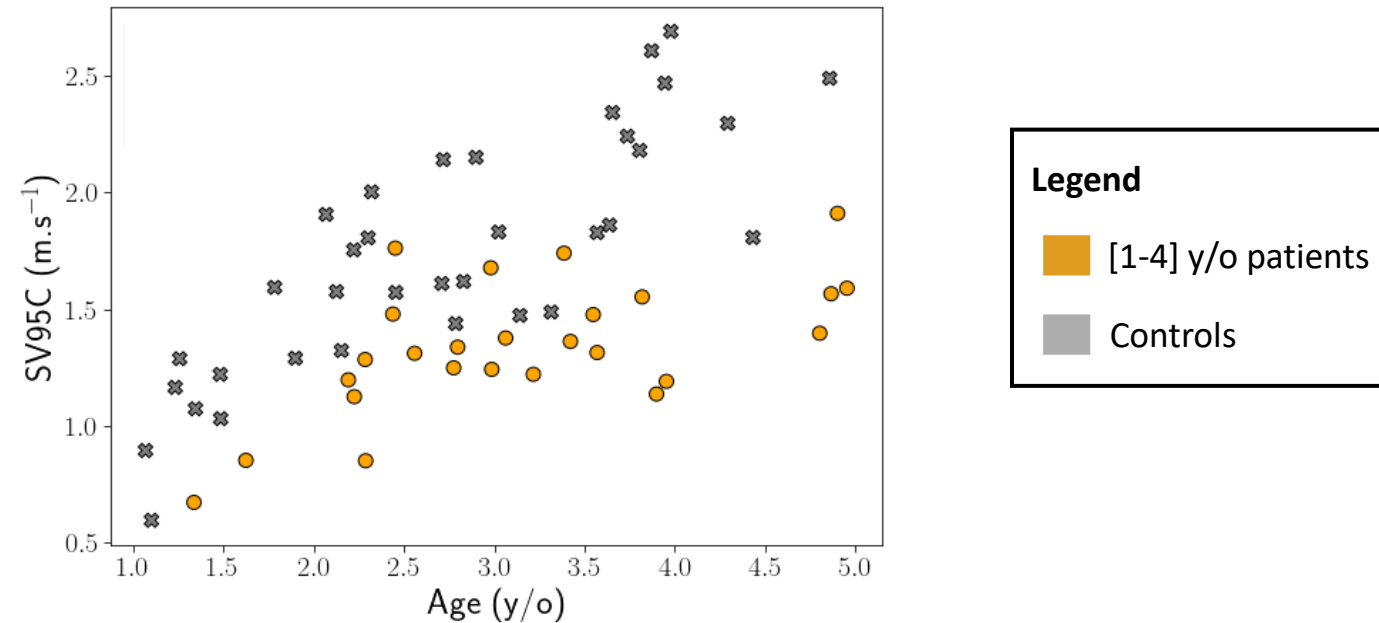
Excellent SV95C reliability for young subjects

Intra-class correlation coefficient (ICC)
between 2 consecutive 2-week baseline recordings

population	N	ICC2K	ICC1
Patient	28	0.99	0.98
Control	35	0.98	0.96

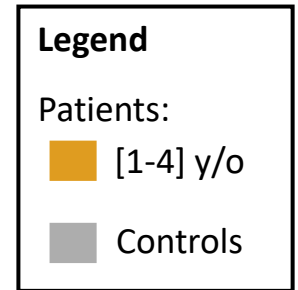
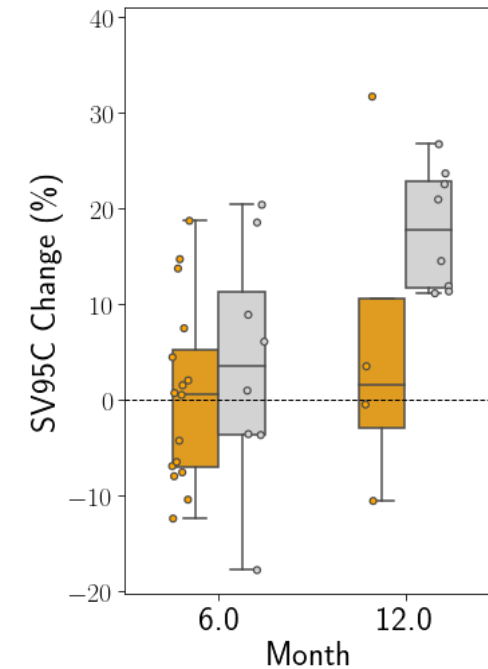
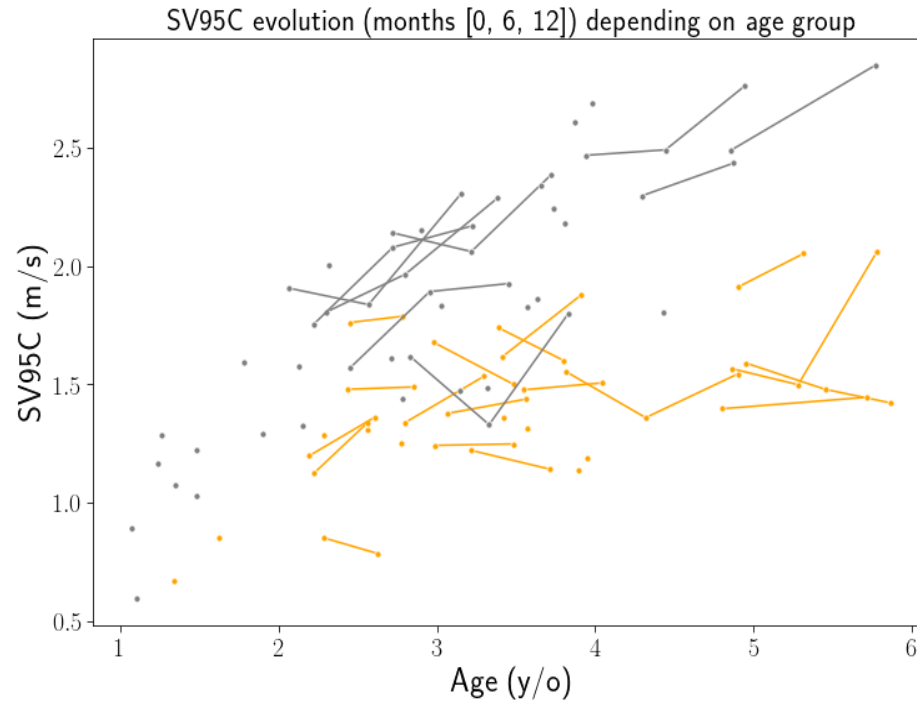
ICC1=intra-class correlation coefficient single-rating, absolute-agreement, 1-way random-effects model; ICC2k=intra-class correlation coefficient mean-rating (multiple raters k = 2), absolute-agreement, 2-way random-effects model; SV95C= stride velocity 95th centile.

Confirmed ability to discriminate patients from controls



SV95C is significantly different between patients and controls ($p < 0.01$)

SV95C change from baseline



Preliminary longitudinal data shows greater SV95C improvement for controls vs. patients

Conclusion

1. Huge attrition rate between academic research and regulatory consideration
2. The qualification process is long- costly and incredibly burdensome
3. The potential is huge across all fields of medicine



The Liege CRMN Team

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Laurie Medard

Manon Duclos

Laura Buscemi

Charline Dubois

Stephanie Delstanche

Aurore Daron

**Margaux
Poleur**





Mélanie
Annoussamy
1974-2023

