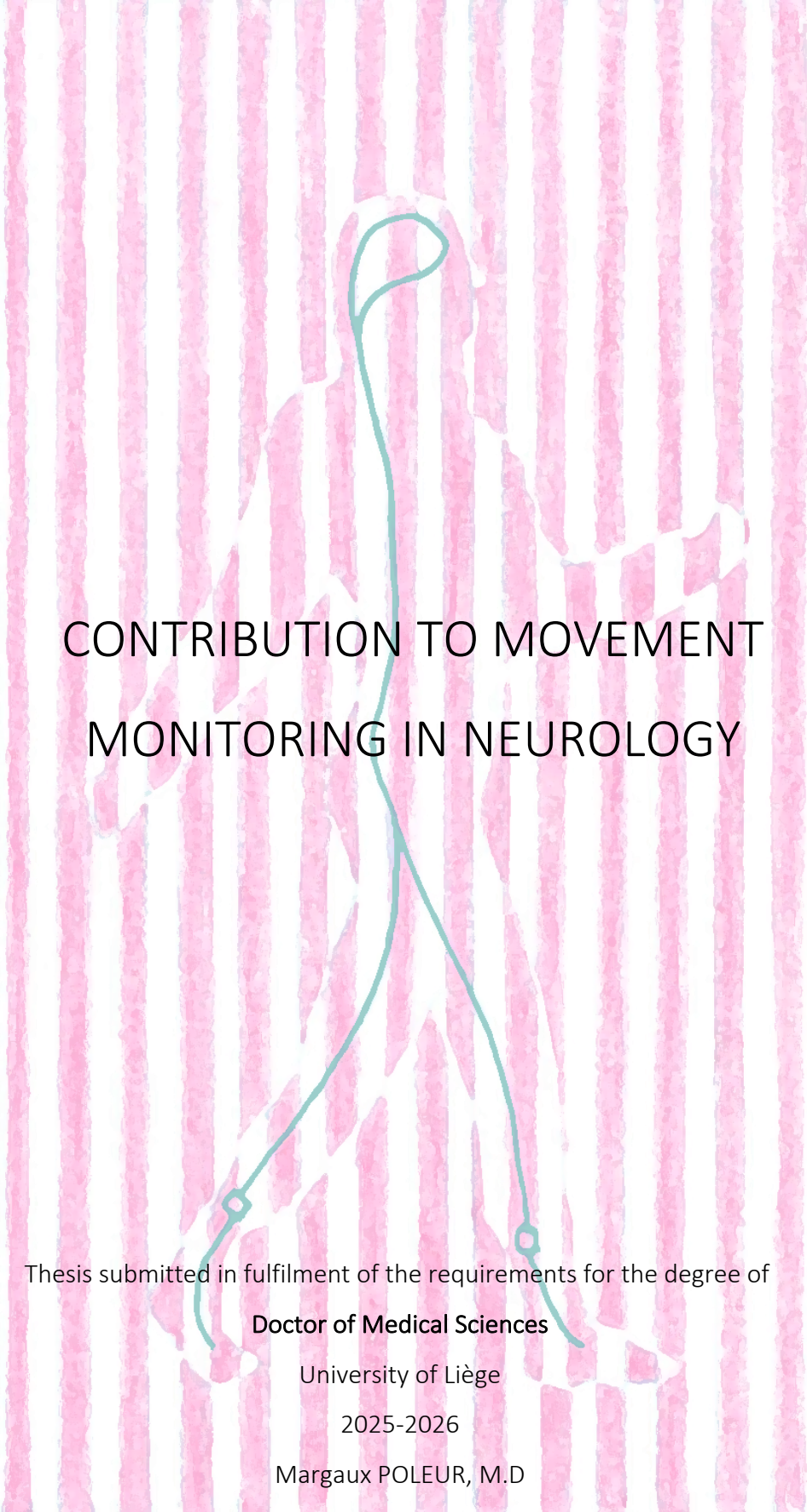




CONTRIBUTION TO MOVEMENT MONITORING IN NEUROLOGY

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“Measure what can be measured
and make measurable what cannot be measured.”

Galileo Galilei

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LIST OF ABBREVIATIONS

4SC: 4-stair climb

6MWD: 6-minute walk distance

6MWT: 6-minute walk test

9HPT: Nine-Hole Peg Test

10MWT: 10-metre walk test

AAV: adeno-associated virus

ADHD: attention deficit hyperactivity disorder

AI: artificial intelligence

ALS: amyotrophic lateral sclerosis

ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

ALSFRS-R GMS: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale gross motor subscore

AIMS: Abnormal Involuntary Movement Scale

AIM-S: Ataxia Instrumented Measures-Spoon

AON: antisense oligonucleotides

APA: anticipatory postural adjustment

ASD: autism spectrum disorder

ATS: American Thoracic Society

AUC: area under the curve

AX3: Axivity accelerometer

BARS2: Brief Ataxia Rating Scale

BBS: Berg Balance Scale

BBT: Box and Block Test

BMD: Becker muscular dystrophy

BMI: body mass index

CAP: CAG-Age Product

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy

CoV: coefficient of variation

CMT: Charcot-Marie-Tooth

DBS: deep brain stimulation

DM: myotonic dystrophy

DMD: Duchenne muscular dystrophy

EDSS: Expanded Disability Status Scale

EMA: European Medicines Agency

EU: European Union

FD: focal dystonia

FDA: U.S. Food and Drug Administration

FN: false negative

FP: false positive

FRDA: Friedreich's ataxia

FSHD: facioscapulohumeral dystrophy

FXS: fragile X syndrome

GLTEQ: Godin Leisure Time Exercise Questionnaire

GM2: GM2 gangliosidosis

GMFM: Gross Motor Function Measure

HD: Huntington disease

HR: harmonic ratio

HSP: hereditary spastic paraplegia

ICARS: International Cooperative Ataxia Rating Scale

ICC: intraclass correlation coefficient

IMI: Innovative Medicines Initiative

IMU: inertial measurement unit

INDIP: Inertial Device for In-Patient reference system

IQ: intelligence quotient

IQR: interquartile range

LCT: L-dopa challenge test

LEDD: L-dopa equivalent dose

L-dopa: levodopa

LPA: light physical activity

LOI: Letter of Intent

LVC: lateral velocity change

MAE: mean absolute error

MCID: minimal clinically important difference

MDS-UPDRS: Movement Disorder Society–Unified Parkinson's Disease Rating Scale

MOBILISE-D: Mobilise-D consortium
 MoCA: Montreal Cognitive Assessment
 MFIS: Modified Fatigue Impact Scale
 MFM: Motor Function Measure
 MG: myasthenia gravis
 MGH: Massachusetts General Hospital
 ML: machine learning
 MMAT: Mixed Methods Appraisal Tool
 MMT: manual muscle testing
 Mocap: motion capture
 MPA: moderate physical activity
 MPS: mucopolysaccharidosis
 MRC: Medical Research Council
 MRD: minimal recording duration
 MS: multiple sclerosis
 MSA: multiple system atrophy
 MSIS-29: Multiple Sclerosis Impact Scale
 MSWS-12: 12-item Multiple Sclerosis Walking Scale
 MVPA: moderate-to-vigorous physical activity

 NA: not applicable
 N/A: not available
 NMRC: Neuromuscular Reference Centre
 NP-C: Niemann–Pick type C
 NSAA: North Star Ambulatory Assessment
 NUCOG: Neuropsychiatry Unit Cognitive Assessment Tool
 Nb strides/h: number of strides per hour

 ORD: optimal recording duration

 PAL: physical activity level
 PD: Parkinson’s disease
 PMS: progressive multiple sclerosis
 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 PSP: progressive supranuclear palsy
 PTI: Postural Tremor Index
 PUL: Performance of Upper Limb
 PWS: Prader–Willi syndrome

QMT: quantitative muscle testing

RDRS: Rush Dyskinesia Rating Scale

RFF: rise from floor

ROM: range of motion

RRMS: relapsing–remitting multiple sclerosis

SARA: Scale for the Assessment and Rating of Ataxia

SBMA: spinal and bulbar muscular atrophy

SCA: spinocerebellar ataxias

SCAFI: Spinocerebellar Ataxia Functional Index

SD: standard deviation

SDMT: Symbol Digit Modalities Test

SEM: standard error of measurement

SL50C: stride length 50th centile

SL95C: stride length 95th centile

SMA: spinal muscular atrophy

SPRS: Spastic Paraplegia Rating Scale

SRM: standardised response mean

SV50C: stride velocity 50th centile

SV95C: stride velocity 95th centile

T25FW: Timed 25-Foot Walk

TFC: Total Functional Capacity

TMS: Total Motor Score

TN: true negative

TP: true positive

TSC: tuberous sclerosis complex

TUG: Timed Up and Go Test

TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale

UHDRS: Unified Huntington's Disease Rating Scale

VPA: vigorous physical activity

VO₂: oxygen consumption

WD90C: walking distance 90th centile

WD95C: walking distance 95th centile

wDHT: wearable digital health technology

WGL: Word Generation List

ABSTRACT

Medicine advances through measurement, and meaningful progress depends on outcome measures that are robust, valid, and sensitive. Conventional clinical assessments remain limited by subjectivity, low sensitivity to change, and poor ecological validity. Wearable digital health technologies (wDHT) address these limitations by enabling continuous and passive monitoring of movement in daily life using body-worn inertial sensors (accelerometers and gyroscopes). They generate objective, ecologically valid, high temporal resolution data. The regulatory acceptance of the stride velocity 95th centile (SV95C) as a primary endpoint in Duchenne muscular dystrophy illustrates the transformative potential of these technologies for clinical research and therapeutic development.

This thesis investigates the role of wDHT in the assessment and monitoring of several neurological diseases. Its main objectives are to identify, evaluate, and contribute to the validation of digital outcome measures capable of reliably capturing disease progression and treatment effects. A systematic methodological framework was applied, combining analytical validation against reference systems (including motion capture) and longitudinal real-world monitoring, to enable a comprehensive psychometric evaluation encompassing accuracy, reliability, validity, and sensitivity to change.

Two systematic reviews provide the scientific basis for this work. The first review analyses 139 studies on digital outcomes in rare neurological diseases, revealing substantial methodological heterogeneity and the limited availability of fully validated digital outcome measures. The second focuses on real-world gait speed measurements that have received or are seeking regulatory approval.

Original multicentre studies were subsequently performed across multiple neurological conditions. A normative reference dataset linking real-world gait variables with demographic and clinical characteristics was established to support comparative analyses with patient populations. In multiple sclerosis, digital outcome measures demonstrated high analytical accuracy, excellent reliability, strong agreement with conventional clinical measures, and greater sensitivity to 12-month disease progression than traditional outcomes in both relapsing-remitting and progressive forms. In amyotrophic lateral sclerosis, stride velocity (SV95C) exhibited remarkable reliability and strong correlations with ambulation-related clinical measures, and high sensitivity to change over 3 and 6 months. In Parkinson's disease, digital outcome measures accurately captured motor symptoms and treatment response during controlled L-dopa challenge testing.

Collectively, these findings establish wearable-derived digital outcome measures as reliable, clinically meaningful, and sensitive markers of neurological disease progression. By enabling precise, real-world measurement of motor function, wDHT represent a paradigm shift in the evaluation and monitoring of neurological diseases. Their integration into clinical research and care can substantially improve the evaluation of neurological diseases, reduce clinical trial duration and sample size, and bring clinical measurement closer to patients' real-life experience.

RÉSUMÉ

Le progrès médical est indissociable de notre capacité à le mesurer de manière rigoureuse, au moyen de critères d'évaluation robustes, valides et sensibles. Cependant, les évaluations cliniques traditionnelles présentent des limites importantes, notamment en raison de leur subjectivité, de leur faible sensibilité au changement et de leur représentativité incomplète des situations de vie réelle. Les outils de médecine digitale permettent de dépasser ces limites en offrant un suivi passif et continu du mouvement dans la vie quotidienne, grâce à l'utilisation de capteurs inertiels portables, tels que les accéléromètres et les gyroscopes. Ils génèrent ainsi des données objectives, de haute résolution temporelle et fidèlement représentatives de la vie réelle. La reconnaissance réglementaire du 95^e percentile de la vitesse de marche (SV95C) comme critère d'évaluation principal dans les essais thérapeutiques portant sur la dystrophie musculaire de Duchenne illustre le potentiel profondément transformateur de ces technologies pour la recherche clinique.

Cette thèse explore le rôle d'un outil de médecine digitale dans l'évaluation et le suivi de plusieurs pathologies neurologiques, avec pour objectifs d'identifier, d'évaluer et de contribuer à la validation de critères de jugement digitaux permettant de mesurer de manière fiable la progression de la maladie ainsi que l'effet des interventions thérapeutiques. Nous avons adopté une approche méthodologique systématique, combinant validation analytique par comparaison à des systèmes de référence et suivi longitudinal en conditions de vie réelle, afin de permettre une évaluation psychométrique complète incluant précision, fiabilité, validité et sensibilité au changement.

Deux revues systématiques de littérature fournissent le cadre de référence scientifique de ce travail. La première revue, fondée sur l'analyse de 139 études, met en évidence une hétérogénéité méthodologique marquée ainsi que le nombre limité de critères de jugement digitaux pleinement validés dans les maladies neurologiques rares. La seconde se consacre à l'analyse des mesures de la vitesse de marche en conditions de vie réelle ayant obtenu, ou recherchant, une qualification réglementaire.

Des études multicentriques originales ont ensuite été conduites dans plusieurs pathologies neurologiques. Une base de données normative a été constituée pour caractériser les paramètres de marche en conditions de vie réelle en fonction de variables démographiques et cliniques, afin de permettre des comparaisons avec différentes populations de patients. Dans la sclérose en plaques, les critères d'évaluation digitaux ont montré une excellente précision analytique, une fiabilité élevée, une forte concordance avec les mesures cliniques conventionnelles et une sensibilité au changement à 12 mois supérieure aux mesures traditionnelles, tant dans les formes rémittentes que progressives. Dans la sclérose latérale amyotrophique, le SV95C présente une fiabilité remarquable, de fortes corrélations avec les mesures cliniques et une sensibilité élevée au changement à 3 et 6 mois. Dans la maladie de Parkinson, les mesures digitales ont permis de quantifier avec précision les symptômes moteurs et la réponse au traitement lors du test à la L-dopa.

Dans l'ensemble, ces résultats positionnent les critères d'évaluation digitaux issus de dispositifs portables comme des marqueurs fiables, cliniquement pertinents et sensibles de la progression dans ces maladies neurologiques. En offrant une mesure précise de la fonction motrice en conditions de vie réelle, la médecine digitale propose un changement de paradigme dans l'évaluation et le suivi de ces maladies. Son intégration en recherche clinique et en pratique médicale pourrait améliorer substantiellement l'évaluation des patients, réduire la durée et la taille des essais cliniques et rapprocher la mesure clinique de l'expérience vécue des patients.

PHD CANDIDATE'S CONTRIBUTION

This thesis is the result of a collaborative research programme involving several researchers and partner institutions. To ensure clarity, all results generated as part of this work are presented within a single manuscript. I formally acknowledge that this research was not conducted in isolation, and that several researchers significantly contributed to the project.

My specific contributions to each part and chapter are outlined below:

PART 1

- ◆ CHAPTER 2 – Focus on Rare Neurological Diseases

I conducted the literature review, conceived and designed the study framework, performed data collection, and wrote the manuscript.

- ◆ CHAPTER 3 – Focus on Real-World Walking Speed

I conducted the literature review, conceived and designed the study, performed data collection, and wrote the manuscript.

PART 2

- ◆ CHAPTER 2 – Normative Data

Most of the data collection was carried out by Ana Ulinici. I contributed to data analysis and wrote the manuscript.

- ◆ CHAPTER 3 – Multiple Sclerosis

I conducted, together with the Neuromuscular Reference Centre (NMRC) research team, the ActiMS Study in Daily Living Conditions, a multicentre longitudinal clinical trial. My responsibilities included study setup and coordination across sites, initiation and opening of study centres, data monitoring, and overall project oversight. I personally recruited and longitudinally followed 34 patients participating in the study. I also conducted and recruited all the participants for the monocentric ActiMS controlled environment study.

In addition, I contributed to data processing and statistical analysis in close collaboration with the engineering team at Sysnav, particularly with Oihanna Piquet. I was responsible for drafting the manuscript.

- ◆ CHAPTER 4 – Amyotrophic Lateral Sclerosis

I recruited and followed 17 patients in the study and participated in data analysis in collaboration with the engineering team at Sysnav.

- ◆ CHAPTER 5 – Parkinson's Disease

Data collection was performed by Teresa Gidaro and Bertrand Degos. I performed data analysis in collaboration with the engineering team at Sysnav and wrote the manuscript of the paper.

1

PART 1

INTRODUCTION

CHAPTER 1

FUNDAMENTAL PRINCIPLES

Effective medicine is defined not by intent, but by measurable results. That's where clinical outcome measures come in. They are the compass guiding us through the complexity of treatment evaluation, helping us distinguish real progress from wishful thinking. By tracking valid, robust, sensitive outcomes, we move beyond presumption and gain evidence-based insights into treatment efficacy. This approach helps ensure that patients receive care that truly makes the difference.

In some rare clinical trials, the impact of a therapy is so dramatic that complex outcome measures become almost useless. When drugs transform the prognosis of children expected to die in their first years, allowing them not only to survive but also to gain independence (Finkel et al., 2025), even the simplest, least sensitive measures could capture the improvement. Unfortunately, most treatments do not produce such a striking effect. Their benefits may be subtle, gradual, non-linear, or highly variable across patients. In these cases, robust, sensitive, and well-validated outcome measures become essential. In their absence, trial outcomes may be misinterpreted, including the occurrence of false negatives, which could lead to the premature discontinuation of the development of promising therapies.

A striking example is the phase III trial evaluating Tofersen in patients with SOD1-associated amyotrophic lateral sclerosis (ALS). Despite promising biological effects, such as reduction of neurofilament levels, the trial failed to demonstrate a clear clinical benefit on the primary endpoint (Miller et al., 2022). This is unfortunate, as the absence of significant efficacy may be due to a lack of sensitivity of selected outcome measures. However, the decision of regulatory agencies to grant approval despite the trial's failure (Food and Drug Administration, 2023) raises important concerns. Allowing a drug onto the market without convincing evidence of proved clinical benefit sends the questionable message that biological efficacy alone is sufficient, even when patients do not measurably improve. This not only undermines the credibility of clinical research but also risks discouraging the rigorous development of therapies. Rather than attempting to "fix" the problem through an approval that calls the entire drug evaluation system into question, we should address the issue upstream by developing and validating outcome measures we can trust.

It is important to underline that imaging and laboratory biomarkers, even if valuable, cannot replace clinical outcomes. Biomarkers may reveal the biological effect of a treatment, but they fail to capture what truly matters to the patients: how they feel or function. An MRI can show changes in tissue, and a blood test can measure a change in protein levels, but neither can tell us whether a patient can walk unaided, whether pain has lessened, or whether independence has been regained. Only clinical outcome measures bridge this gap, translating biological change into meaningful, patient-centred benefit.

The objective of this thesis is to identify, evaluate, and contribute to the validation of digital outcome measures that can be used to monitor neurological diseases affecting motor function. To reach this objective, we investigate a range of neurological diseases through studies of different designs, each tailored for the specific clinical and methodological challenges of each condition. The results of these investigations are presented in separate chapters in the second part of the manuscript, following a common introduction that outlines the conceptual foundations of our work and explains the underlying technologies. The thesis concludes with a general discussion reviewing our contributions and highlighting the next steps required to advance digital outcome measures towards full validation, regulatory acceptance, and possibly one day the widespread adoption of the monitoring of motor function in neurological research and care.

I. DIGITAL BIOMARKERS, DIGITAL OUTCOMES AND REGULATORY QUALIFICATION

Digital biomarkers have been defined by the European Medicines Agency (EMA) as an objective, quantifiable measure of physiology or behaviour used as an indicator of a biological or pathological process, or a response to an exposure or an intervention that is derived from a digital measure (e.g., step length) (European Medicines Agency, n.d.-a).

As defined by the U.S. Food and Drug Administration (FDA) (Food and Drug Administration, n.d.-a), a clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives. This notion is mostly applied to quantify the impact of an intervention aiming at modifying the course of a disease and its effects (*Outcome Measures and Case Definition*, n.d.).

In other words, digital biomarkers correspond to derived metrics based on measurable variables (e.g., mean stride velocity derived from gait speed) that reflect underlying biological or pathological processes, whereas digital outcomes are validated digital biomarkers used to assess a patient's condition, disease progression, or treatment efficacy within a defined clinical context.

Therefore, digital biomarkers can be used as outcomes, provided they are validated for their intended purpose. An outcome is regarded as validated when it has been rigorously examined in adequately designed and well-controlled studies, demonstrating consistent reliability, validity, sensitivity to change (Goldsack et al., 2020). This process requires a full characterisation of their psychometric properties, beyond the preliminary findings of original discovery studies. Outcome qualification is a longer and more codified process through which authorities such as the FDA or EMA formally qualify an outcome measure within a well-defined context of use (Food and Drug Administration, n.d.-a).

II. OUTCOME ASSESSMENT AND PSYCHOMETRIC PROPERTIES

Psychometric properties refer to scientific criteria used to evaluate the quality of measurement tools, such as questionnaires, scales, or tests. These properties determine how well an instrument captures what it is designed to measure, and whether its results are reliable, valid, sensitive to change, and meaningful. Basically, psychometric properties provide the foundation for trust in measurement tools.

As one of the main goals of this thesis is to contribute to the validation of digital outcomes in various neurological diseases, psychometric properties serve as a fundamental framework guiding this work. It is therefore essential to define and discuss some of these properties as part of the introduction.

Accuracy describes how close a measurement is to the accepted reference value. In the context of digital outcome measures, this typically refers to how precisely the device or algorithm measures the targeted variable (e.g., walking speed) compared to a reference standard, such as motion capture systems (Goldsack et al., 2020).

Reliability refers to the consistency and stability of a measurement under identical conditions. Reliability can be assessed in different ways (Mokkink et al., 2010). Test–retest reliability assesses the stability and reproducibility of scores obtained from the same measure when administered on separate occasions under equivalent conditions. Inter-rater reliability assesses the degree of agreement between different raters, while intra-rater reliability evaluates the consistency of a single rater across repeated assessments (Allied Health Professions Outcome Measures UK Working Group, 2019). However, in the context of continuous monitoring of movement, inter-rater and intra-rater reliability are not relevant, since we use objective tools and the measurement does not depend on a rater. Instead, reliability can be approximated by comparing different segments of the same continuous recording period, a strategy that can serve as a proxy for test–retest reliability.

Validity refers to the degree to which a measurement tool accurately records what it is intended to measure (Mokkink et al., 2010). Several forms of validity are recognised. We mainly used known-group validity measures, defined as the ability to differentiate between controls and patients, between patients with different levels of disability, or between patients with different conditions, as well as construct validity, evaluated through correlations with gold standard outcomes. Predictive validity, which reflects a measure’s ability to predict future outcomes or behaviour, and content validity, which ensures that the items included fully represent the construct of interest (Allied Health Professions Outcome Measures UK Working Group, 2019) will be addressed as next steps in the discussion section, as they represent important yet challenging milestones in outcome measure evaluation.

Sensitivity to change indicates an outcome’s ability to detect slight but meaningful changes over time, especially in disease progression or response to intervention (Mokkink et al., 2010). It includes the assessment of floor and ceiling effects, which occur when an outcome measure lacks the sensitivity to change at the extreme low or high ends of the measure (Allied Health Professions Outcome Measures UK Working Group, 2019).

Another important property is interpretability, defined as the extent to which qualitative meaning can be assigned to quantitative scores, such as understanding what a change of 3 points on a scale clinically represents in clinical terms (Mokkink et al., 2010).

Feasibility, sometimes considered in parallel with psychometric properties, assesses the extent to which a tool is suitable for use in a specified manner and for a specified purpose (Slade et al., 1999). In the context of wearable digital health technology (wDHT), feasibility reflects how practical and acceptable a device is for use in daily living. It encompasses factors such as usability, participant burden, data completeness, and compliance. The feasibility of an assessment indicates whether the tool can be effectively integrated into clinical or research practice.

III. WEARABLE DIGITAL HEALTH AND MAGNETO-INERTIAL TECHNOLOGIES

Wearable Digital Health

Wearable digital health refers to the use in healthcare of sensor-based devices worn on the body (such as smartwatches, insoles or patches containing sensors) with the aim of continuously monitoring, collecting, and analysing physiological data.

In recent years, an increasing number of technologies have been used for remote health monitoring (Piwek et al., 2016). The rapid adoption of wDHT could be explained by advances in miniaturised wireless sensors making it feasible to shift healthcare from in-clinic to a field approach. These technologies are increasingly being used not only by individuals to improve their lifestyle (Demandsage, n.d.) but also by clinicians and researchers to support diagnosis, disease progression and treatment monitoring. The higher temporal resolution and real-world relevance of digital outcomes derived from these devices potentially provide significant advantages over conventional assessments, which are often limited to periodic in-clinic visits and subjective evaluations. Furthermore, wDHT could facilitate the assessment of clinical domains including those that have historically been difficult to quantify (such as real-life mobility).

Magneto-inertial Technology

Remote monitoring of neurological diseases generally relies on two main approaches. The first is task-based assessment, which uses apps or video recordings. The second is passive monitoring, mainly through wDHT, which continuously and unobtrusively capture spontaneous movement in daily living. Passive monitoring can address several limitations of task-based methods, including susceptibility to motivational influence and learning effects. In addition, studies in Parkinson's disease (PD) have reported a potentially higher compliance when using passive monitoring (Bloem et al., 2023). By enabling larger sample sizes through continuous data collection, passive monitoring also reduces the impact of day-to-day variability (Warren et al., 2010). Accordingly, this manuscript focuses exclusively on passive monitoring approaches and does not discuss task-based assessments.

The increasing interest in wDHT (Masanneck et al., 2023) within neurology has primarily focused on high-prevalence neurological disorders, particularly those with motor symptoms such as PD (Moreau et al., 2023a) and

multiple sclerosis (MS) (Alexander et al., 2021; Woelfle et al., 2023). This trend is largely explained by the availability of wearable sensors capable of tracking motor functions and by the relatively large patient populations that facilitate clinical studies.

The most common wearable sensors used in neurological diseases are accelerometers and gyroscopes (Prasanth et al., 2021; Yang & Hsu, 2010). A triaxial accelerometer measures linear acceleration along three perpendicular axes (x, y, and z), while a triaxial gyroscope measures angular velocity around these same three axes (Ní Scanail et al., 2006). Together, they provide information about an object's motion and orientation in three-dimensional space. A magnetometer is a sensor that measures both the strength and direction of the Earth's local magnetic field (Wittmann et al., 2019). All these sensors can be combined into a single sensor known as an inertial measurement unit (IMU), where the magnetometer functions as a compass.

Unfortunately, this technology is subject to measurement error. As stated earlier, accuracy refers to the comparison with a reference gold standard (motion capture). The error refers to the difference between the measurements obtained by the digital technology and those obtained from the gold standard system. A major source of error is gyroscopic drift, which accumulates over time (Wittmann et al., 2019). The magnetometer can partially compensate for this drift by providing a reference, although its effectiveness is reduced in environments with magnetic disturbances (Wittmann et al., 2019). While we can apply precautionary measures to minimise magnetic disturbances in laboratory settings, such control is, however, not possible in daily living recordings.

Patients can wear one or several sensors, which can be attached to various parts of the body. Both the number of sensors and their location determine not only which movements can be recorded but also the precision of the collected data. A single sensor can capture the movement of the body segment to which it is attached, and in some cases infer related movements of other parts of the body. For example, an IMU placed on the wrist can capture hand motion or provide information about walking cadence. However, it cannot precisely characterise detailed gait patterns, nor can it accurately differentiate the motion of individual joints within the upper limb. Additional sensors can be added for a few purposes: to record different aspects of movement (e.g., upper-limb and gait evaluation) and to improve data quality either by eliminating unwanted movement (e.g., removing body movement during upper-limb analysis) or by improving the ability to reconstruct movement (e.g., providing greater granularity in distinguishing between walking, running, or stair climbing). At one point, the use of multiple sensors could provide near-kinematic reconstruction, allowing precise estimation of joint angles, gait phases, and limb coordination. However, temporal synchronisation is critical when several sensors are used, as even a small desynchronisation can distort movement reconstruction. Achieving near-perfect synchronisation remains challenging with wireless technology (Chen et al., 2022).

In real-world applications, a compromise exists between precision and practicality. Adding more sensors generally provides greater insight into movement analysis but it also increases complexity, cost, and the burden for the patient. More sensors raise concerns about patient adherence, as continuously wearing a large number of sensors, especially wired ones, can be burdensome and alter the spontaneous individual behaviour. For research protocols,

the choice of the number of sensors and placement should be guided by the objective and the context of use. At the present time, multiple sensor networks are mainly limited to use in movement analysis laboratories, where they can precisely characterise patients' mobility, but they are not practical for real-world remote monitoring. For long-term or real-world studies, it is essential to balance data quality with patients' comfort and to adopt a "minimal" configuration of one or two sensors (Woelfle et al., 2023).

The position of the sensors also plays a critical role. Placement on distal segments can capture fine or rapid movement at the wrist and precise stride characteristics at the ankle (Borzi et al., 2025; Pacini Panebianco et al., 2018), but offers little information about the trunk or proximal joints. Proximal placement of wearable sensors over the waist or trunk is better suited to assess postural sway (Zampogna et al., 2020). For instance, in the context of our research, a single sensor placed on the wrist or waist is sufficient to monitor overall activity (Brand et al., 2024) but is inadequate for capturing detailed gait metrics (Jimenez-Moreno et al., 2019). This highlights the important distinction between parameters that a sensor can directly measure and those that must be inferred.

Finally, sensor characteristics also include more technical and ethical issues that are equally important for recorded data but are rather of the concern of the engineer or the device's owner. Sampling frequency should be sufficient for the movement type, higher for rapid movements or tremors and lower for general activity monitoring. Calibration across a range of temperatures, pressures, and dynamic environments is essential to reduce measurement errors and variability. In addition, the device's resistance to external aggression, such as water exposure, humidity, dust, and mechanical shocks, is essential to ensure durability and data integrity in real-world conditions. Power consumption, data storage, and data transfer including ethical and privacy considerations should also guide study design and data management.

In summary, remote monitoring of neurological diseases with wearable sensors requires careful methodological considerations, considering the number, location and technical characteristics of the sensors, as well as the study design and the condition under investigation. Ultimately, the choice of sensor type, placement, and configuration must balance precision and feasibility to provide clinically meaningful data while minimising burden.

Basic Concepts of Gait Analysis

Gait analysis relies on the correct identification of its major phases, depicted in Figure 1. Gait analysis is the study of walking patterns which can be quantified using cumulative activity parameters such as step count or spatiotemporal gait parameters, such as stride length, stride speed, stance/swing time or percentage.

Gait analysis was traditionally conducted in a dedicated laboratory using cumbersome equipment, which has limited its application in daily living (Prasanth et al., 2021). Furthermore, previous data suggest that laboratory assessments may not always accurately reflect real-world gait patterns (Antonellis et al., 2025; Takayanagi et al., 2019).

Magneto-inertial technology can be used to assess ambulation in daily living. Devices derived from this technology range from simple step counters to sophisticated multisensory systems (Dobkin, 2013). Unlike consumer devices,

medical devices must demonstrate validated measurement accuracy, sensitivity, and specificity (Caulfield et al., 2019). However, most outcomes are measured using consumer-available actimeters, which primarily capture step count but have limited ability to reliably provide stride-level data (Micó-Amigo et al., 2023).

Advances in inertial sensors and signal analysis have improved the precision of human movement analysis (van Unnik et al., 2024). They provide a unique opportunity for the identification and measurement of individual strides during normal daily living (Michaud et al., 2024) rather than relying on estimates of patient activity. This represents a significant advancement for wDHT beyond the simple metric of “steps per day” or even walking bout measures. Shifting from basic step counting to detailed stride analysis potentially provides a deeper and more clinically valuable understanding of human ambulation.

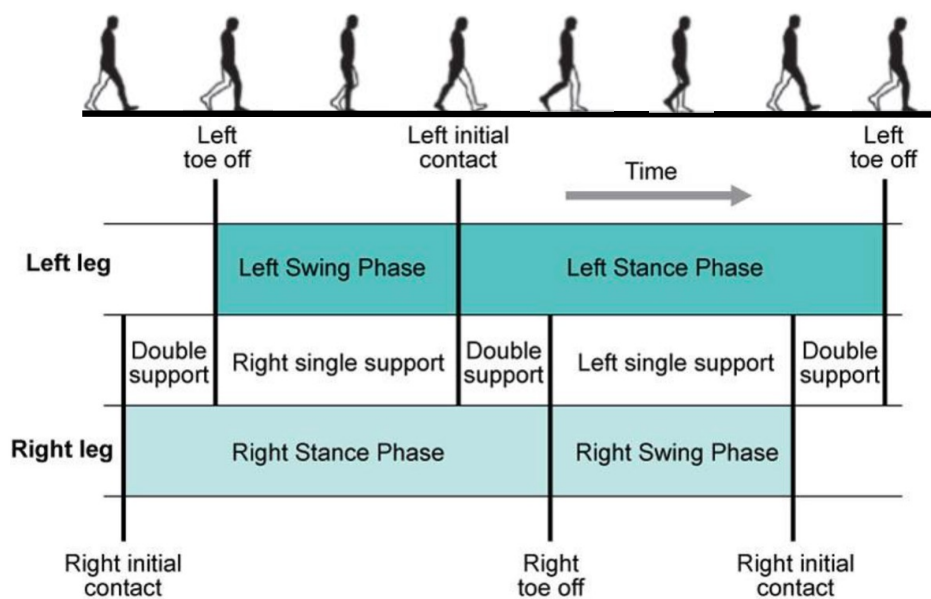


Figure 1. Human gait cycle (adapted from Levine D, 2012).

Overview of Applications in Neurology

The use of wDHT is still in its early development stages, yet research over the past decade has explored several applications, with many more anticipated in the coming years (Lu et al., 2020a). Further details and potential applications will be discussed in the general discussion section.

At the present time, the most advanced and straightforward application of wDHT in neurology is event detection. Although this represents a focus distinct from the present work, this approach is already well established in clinical practice for seizure monitoring in epilepsy (Donner et al., 2024) and sleep medicine (DE Zambotti et al., 2019). In epilepsy, it relies on cerebral activity monitoring, while in sleep assessment it combines cerebral activity with additional physiological signals, rather than focusing on the detection of motor events alone.

As for the detection of motor events, PD is probably the condition in which the most significant progress has been made. In this condition, the use of wDHT has already demonstrated valid, reliable, and sensitive assessments of motor symptoms, capturing real-world fluctuations and treatment-related changes with strong agreement with clinical evaluations (Mahadevan et al., 2020). One study suggests that in-clinic assessments may fail to reflect the patients' motor status at home (Burq et al., 2022). Moreover, a blinded, controlled trial showed statistically significant improvements on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total, III, and IV scales in the group using objective measurements compared with the conventionally treated group (Woodrow et al., 2020a). In PD, the detection of freezing of gait has also received increasing attention (Silva de Lima et al., 2017). Additionally, there is an interest in clinical research for fall detection not only in PD, but also in MS, stroke, Alzheimer's disease (Bonanno et al., 2025), Huntington disease (HD) (J. Adams et al., 2020) and even in the elderly (Subramaniam et al., 2022). These applications highlight the potential of wearable devices to complement traditional clinical evaluations with real-life data that were only accessible until now, through patient self-reports. Together, these findings provide strong support for the added value of real-world symptom monitoring.

Except for PD, the main function assessed in neurological disease is physical activity (Woelfle et al., 2023). Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (Okely et al., 2021), including activities of daily living and exercise. Despite its clinical importance, physical activity remains highly dependent on external factors such as motivation, environment, or weather conditions. Gait, in contrast, is defined as the pattern of walking, representing a complex, cyclic, and coordinated movement involving multiple systems (Levine D, 2012). It is a well-established concept of interest in medicine because of its close relationship to functional independence (Mirelman et al., 2018). We found in the literature many studies exploring gait in real-life settings using wDHT, with a wide range of outcomes and disease-specific focuses (Rozin Kleiner et al., 2019; Silva et al., 2024; Weizman et al., 2021; Woelfle et al., 2023). However, as it will be confirmed by the systematic reviews presented in the next chapters, most of these studies remain small-scale and exploratory. Significant efforts are still needed to clarify how these technologies can be standardised and integrated for interventional purposes in clinical practice and clinical trials.

In clinical trials, remote monitoring provides the opportunity for more reliable and sensitive outcome measures, which can reduce cohort sizes and time-to-endpoint (Youn et al., 2021). A landmark example is stride velocity 95th centile (SV95C), which represents the fastest 5% of strides taken by a patient in daily life, that has become the first digital endpoint to achieve regulatory qualification for use in pivotal clinical trials in Duchenne muscular dystrophy (DMD). This milestone highlights the transformative potential of wDHT to influence clinical trial design and therapeutic evaluation, a topic that will be discussed in greater detail later in this manuscript.

In this section, we have discussed the main applications of wDHT, especially magneto-inertial devices, in the field of neurology. In the next chapter, we focus specifically on the use of digital outcomes in rare neurological diseases. Although previous research has primarily focused on more common conditions, sensitive digital outcomes may

offer unique added value for rare diseases, as discussed in the chapter. Finally, chapter 3 will present the results of a systematic review on well-validated outcomes that capture real-world walking speed, a key parameter of gait.

IV. KEY INSIGHTS

Clinical outcome measures, rather than intention or biomarkers alone, are essential to determine the impact of medical interventions. Most treatments produce subtle or variable benefits, making robust, validated, and sensitive outcomes crucial to accurately assess their efficacy. Digital outcome measures derived from wDHT, including magneto-inertial sensors allow for continuous, objective, monitoring of motor function in neurological diseases, providing greater real-world relevance and higher temporal resolution than traditional in-clinic assessments. Key considerations for the evaluation of these tools include psychometric properties (accuracy, reliability, validity, sensitivity to change, interpretability, and feasibility) and methodological choices regarding the number of sensors, position, and technical characteristics. Early applications in neurology demonstrate the potential of wDHT for symptom monitoring and event detection.

FOCUS ON RARE NEUROLOGICAL DISEASES

The information presented in this section is derived from a systematic literature review entitled “The use of digital outcome measures in clinical trials in rare neurological diseases: a systematic literature review” by M. Poleur et al., published in Orphanet Journal of Rare Disease. This article is not reproduced in its entirety.

I. INTRODUCTION

In the European Union (EU), a disease is defined as rare if it affects fewer than five in 10,000 people across the EU (European Medicines Agency, n.d.-b). In the United States, the Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States (Food and Drug Administration, n.d.-b). Around 10,000 rare diseases have been identified according to these different definitions and about 5% of the European population is thought to be affected by one of them, many of which have neurological manifestations. These diseases are often associated with high mortality and disability, which result in large societal costs (Ferreira, 2019). Drug development for rare diseases is especially challenging due to the small number of subjects eligible for inclusion in clinical trials. Trials in this field tend to be small, single-arm, non-randomised, and open label (Bell & Tudur Smith, 2014). In clinical trials for rare diseases, outcome measures are often subjective, depending on both patient motivation and rater (Alfano et al., 2014). Moreover, test results only reflect the patient’s condition at a specific timepoint, and severity of symptoms often varies with time.

Nevertheless, the precision and the objectivity of the outcome measures are critical (Rath et al., 2017). For most rare diseases, clinical outcomes have not been qualified or validated to the same rigour, or methodological approach and in large cohorts as they have in more common diseases. Digital biomarkers could, to a certain extent, fill this unmet need.

Efforts to develop digital outcome measures have focused mostly on neurological disorders that are not classified as rare (Sica et al., 2021; Vienne-Jumeau et al., 2020), but these measures are increasingly used to evaluate patients who have rare diseases. The use of digital outcome measures is expected to increase with the development of innovative technologies and artificial intelligence (AI) (Ricotti et al., 2023).

In neuromuscular disorders, a recent literature review highlighted the increasing use of sensors to assess motor activity in the real-life and the ability of these sensors to overcome many issues of traditional evaluations (Bortolani et al., 2022). Nevertheless, only one digital outcome measure, the SV95C, is currently qualified by a regulatory agency for use in DMD (Haberkamp et al., 2019).

The purpose of this systematic review is to summarise the current state of progress with regard to the use of digital outcome measures for real-life motor function assessment of patients affected by rare neurological diseases. We also summarise the psychometric properties that have been assessed for each outcome providing a snapshot of where we stand currently in the process of developing and qualifying digital outcomes in rare diseases.

II. METHODS

Before formulating the search strategy, the lead authors (MP, TM) independently created a selection of all rare diseases with neurological manifestations using the list:

https://ec.europa.eu/health/archive/ph_threats/non_com/docs/rdnumbers.pdf (last accessed on January 25th, 2023).

Any disagreement between the reviewers was resolved with the assistance of a third reviewer (LS). We included only rare diseases with a prevalence equal or higher than 1/100,000 and we excluded general terms (e.g., autism spectrum diseases).

Then, we conducted a review of the literature using a comprehensive search of 2 databases (MEDLINE via Ovid and EMBASE electronic databases) and pre-defined selection criteria. Our search strategy intended to capture studies using a technology-based device with potential for remote monitoring of muscle strength and motor function of humans affected by rare neurological diseases. The literature search and analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA). The search strategy is explained in our published protocol, available at the International Prospective Register of Systematic Reviews (Registration: CRD42021281236).

We searched Medline via Ovid and Embase on June 1st, 2021, and we last updated our search strategy on November 30th, 2022. We included all studies with published results in the last 10 years (from June 1st, 2011, to November 30th, 2022) in English. After running the search strategy, citations of all the selected papers were uploaded to Mendeley. Duplicates were manually eliminated.

Two independent reviewers (MP, TM) without conflict of interest reviewed the titles and abstracts of all potentially eligible articles. Any disagreement between the reviewers was resolved with the assistance of a third reviewer (LS).

All previously selected articles were fully reviewed by two investigators to decide if they met the eligibility criteria (available at the International Prospective Register of Systematic Reviews). The two reviewers compared their findings and recorded the reason for exclusion. Potential disagreements were resolved by consensus or, if necessary, with the involvement of a third investigator (LS).

Study characteristics related to publication (authors, title, year of publication) and study design (population characteristics, devices, recorded parameters, experimental set up, main findings) were extracted. One assessor

(MP) extracted and digitally registered this information using Microsoft Office Excel. Another assessor (TM) verified the extracted data from all included articles. Selected papers were clustered according to the disease.

We performed risk of bias assessment of the included studies, using the Mixed Methods Appraisal Tool (MMAT).

III. RESULTS

Selection of Clinical Studies

This review provides a summary of the use of digital outcome measures in clinical trials listed in Medline and Embase. Figure 2 is a flow chart of the process used for inclusion of clinical studies in our analysis. Our search of published literature identified 3826 records, of which 139 were included. Amongst these studies, 51 focused on neuromuscular disorders, 42 on movement disorders, 16 on genetic ataxias, 9 on multisystemic rheumatological diseases, and 21 miscellaneous neurodevelopmental disorders. Information on study designs and collected data are summarised in Table 1.

Disease	Population		Study design			Type of device				Setting		Parameters assessed				
	Number of studies	Number of patients	Interventional	With Controls	Longitudinal	Accelerometer/gyroscope	EMG	App/Software	Other	Home	Controlled environment	Physical activity	Gait Analysis	Upper Limb	Tremor	Other
DMD	18	550	2	7	6	17		2		13	5	10	2	5		5
ALS	15	2323	2	4	8	10	2	4	1	8	8	5	1	3	1	7
CMT	6	392		2	1	6				4	2	4	1		1	
DM	4	142		3		3			1	2	2	1	3	1		2
FSHD	4	70	1	1	2	4		1		2	2		3	3		
MG	2	60		1		2				2		2				
SMA	1	81			1	1				1				1		
SBMA	1	54	1		1	1				1		1				
HD	26	738 (+ 98 premanifest)	3	23	6	23		3		10	19	8	10	4		14
PSP	7	112	1	5	1	7					7		4			3
FD	9	414	1	3		7	2		4		9			1	5	3
SCA	9	322 (+ 80 premanifest)		8	1	9				2	8	1	6	1		4
HSP	3	143		1	1	3					3		3			
FXS	2	38 (+15 premanifest)		2		2					2		2			
FRDA	2	43		2	1	2		1	1	1	2		1	2		1
Sarcoidosis	5	793		1		5				5		5				
Dermatomyositis	3	79		2		3				3		3				
Scleroderma	1	27		1		1				1		1				

PWS	8	143	2	5	2	8				5	3	5	3			2
Pompe disease	2	54			1	1	1		1	2	1	1				1
MPS	1	8		1		1				1		1				
Fabry	1	17		1		1				1		1				
GM2	1	8			1			1	1	1		1				
NP-C	2	22				2				2		1				1
Rett syndrome	5	150	1		1	5				4	2	5				
TSC	1	30				1					1	1				1
Narcolepsy	1	56				1				1		1				
Number of studies	139	6590	14	73	34	126	5	12	7	72	76	58	39	20	7	43

Table 1. Summary by disease of number of studies and their design, population and main findings. *Abbreviations: amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth disease (CMT), myotonic dystrophy (DM), Duchenne muscular dystrophy (DMD), electromyography (EMG), facioscapulohumeral dystrophy (FSHD), focal dystonia (FD), fragile X syndrome (FXS), Friedreich ataxia (FRDA), GM2 gangliosidosis (GM2), hereditary spastic paraplegia (HSP), Huntington disease (HD), myasthenia gravis (MG), mucopolysaccharidosis (MPS), Niemann–Pick type C (NP-C), Prader–Willi syndrome (PWS), progressive supranuclear palsy (PSP), spinal and bulbar muscular atrophy (SBMA), spinal muscular atrophy (SMA), spinocerebellar ataxias (SCA), tuberous sclerosis complex (TSC).*

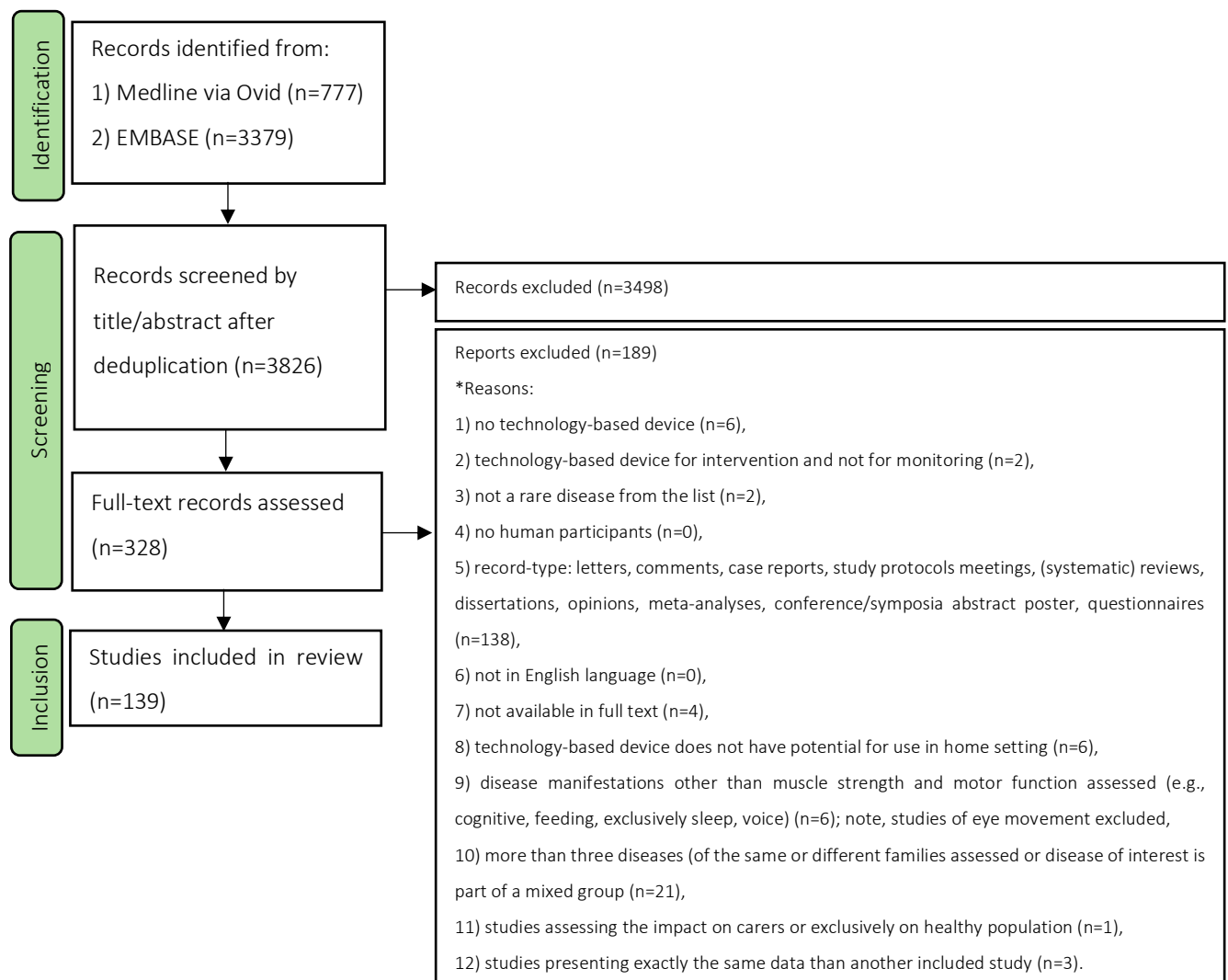


Figure 2. Flow chart of the selection process.

Types of Outcomes

In the studies evaluated, very few outcomes were precisely defined and even fewer were completely validated and ready for qualification. Event detection or frequency directly derived from sequential detection of an event was often measured. Physical activity was measured in various ways including number of steps and time spent in different levels of physical activity. Outcomes related to gait ranged from time-distance variables (i.e., stride length, velocity) to more elaborated variables resulting from machine learning (ML) approaches. Methods for upper limb assessments were also heterogeneous. Other functions monitored included balance and body sway.

Choice and Position of the Sensors

Wearable or portable devices based on inertial technology were by far the most frequently used sensors, although pressure or surface electromyographic sensors were also employed. Technologies included applications and

software. Critical to effective motor assessment is the number and position of the sensors as sensors only assess the movement of the segment where they are placed, and sensor number and position may influence patient compliance. There was large variability in the numbers and positions of sensors in the same patient populations. The locations of the sensors and the numbers of relevant studies are presented in Figure 3.

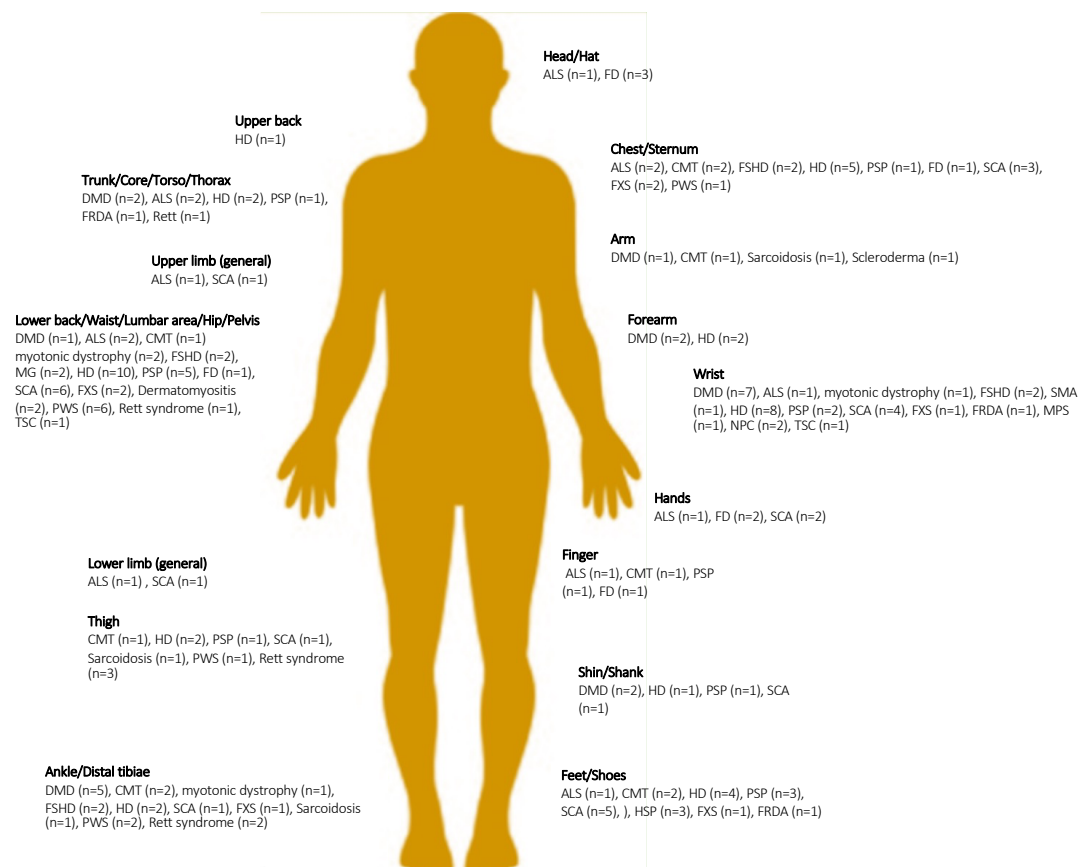
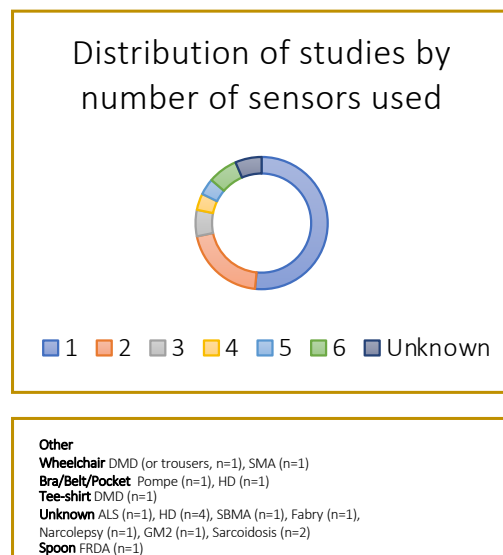


Figure 3. Numbers and placements of wearable and portable inertial sensors. *Abbreviations: amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth disease (CMT), myotonic dystrophy (DM), Duchenne muscular dystrophy (DMD), focal dystonia (FD), Friedreich ataxia (FRDA), facioscapulohumeral dystrophy (FSHD), fragile X syndrome (FXS), GM2 gangliosidosis (GM2), Huntington disease (HD), hereditary spastic paraplegia (HSP), myasthenia gravis (MG), mucopolysaccharidosis (MPS), Niemann–Pick type C (NP-C), progressive supranuclear palsy (PSP), Prader–Willi syndrome (PWS), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxias (SCA), spinal muscular atrophy (SMA), tuberous sclerosis complex (TSC).*

Psychometric Properties

Psychometric properties that were evaluated in this review are summarised in Table 2. We found 92 studies that described use of psychometric evaluation. Most focus on validity assessment through correlation with standard outcomes and distinction between normal and pathological while reliability and sensitivity to change were assessed in only 16 and 21 studies, respectively.

Disease	Validity	Reliability	Sensitivity to negative change	Sensitivity to positive change
Actigraph, Motionlogger Watch, Ambulatory Monitoring, Ardsley, NY, USA				
DMD	Proportional integration mode score correlated with 6MWD and knee extension strength (Kimura et al., 2014).			
Actimyo, Sysnav, Vernon				
DMD	For the MoviPlate and BBT, all variables correlated with the functional scores. Norm of the angular velocity, power, elevation rate correlated with the Minnesota scores and the writing task. The mean of the rotation rate and mean of the elevation rate had the best correlations with task scores (Le Moing et al., 2016).	All ActiMyo variables showed high to very high reliability as assessed using ICC values. The mean of the rotation rate and mean of the elevation rate had the best reliability scores (Le Moing et al., 2016).		
SMA	MFM 32 and grip strength were found to have high correlations with wrist acceleration (Annoussamy et al., 2021).		Wrist angular velocity, the wrist acceleration, the wrist vertical acceleration and power decreased significantly over 6 and 12 months as measures in patients with Type 2 SMA and non-ambulant with Type 3 (Annoussamy et al., 2021).	

FSHD	Strong correlations between representative (stride length and velocity) gait variables and MMT variables were observed (Gidaro et al. 2022).	All the measurements showed high reliability according to ICC values (all >0.9). Representative variables showed lower SEMs (all <0.03) compared to cumulative variables (40.2 and 28.5) (Gidaro et al. 2022).	Significant decline for median speed, SV95C and SL95C at 3 months. The SRM of median speed, SV95C and SL95C was significantly elevated at 3 months (Gidaro et al. 2022).
ActivPal, PAL Technologies Ltd, Glasgow, UK			
Sarcoidosis	Patients with sarcoidosis had lower daily step count than controls and a trend towards fewer sit-to-stand transitions each day. 6MWD correlated with the daily step count (Cho et al., 2019).		
Dermatomyositis	Patients with inactive disease had lower physical activity levels compared with controls (Berntsen et al., 2019).		
Rett syndrome			The sedentary time was decreased after intervention. Positive effects with small to medium effect sizes were seen in sedentary time (Stahlhut et al., 2020).

Actiwatch 2 (AW2), Philips Respironics, Bend, Oregon				
DMD	Habitual daytime activity level was associated with 6MWT performance (Siegel et al., 2020).			
AD_BRC sensor				
HD	Sensor-derived velocity was significantly higher in healthy controls and premanifest HD when compared to HD. Step and stride length were significantly longer in controls and premanifest HD when compared to HD. Significant differences between subject groups across all four balance tasks were observed (Dalton et al., 2013)			
AIM- system				
FRDA	Smoothness, trajectory length, duration, and ROM were the most effective to distinguish individuals with FRDA from controls. The AIM-S score strongly correlated with the mFARS score and the NeuroUL score (Corben et al., 2021).	The AIM-S score showed good to excellent test–retest reliability (Corben et al., 2021).	The sensitivity of the AIM-S to detect deterioration in upper limb function was greater than other measures (Corben et al., 2021).	The AIM-S score showed minimal variability (Corben et al., 2021).
ASUR-Autonomous Sensing Unit Recorder + Physilog				
DMD	Except cadence, all gait parameters showed significant differences between patients and controls. All gait parameters were more affected in the moderate group compared to the mild group. Moderate correlations between the MFM and stride velocity,			

cadence and spectral entropy were observed (Ganea et al., 2012).		
		Duration of walking episodes and the succession of two or three walking episodes lasting more than 30 seconds improved after prednisolone treatment (Jeannet et al., 2011).
Biopack		
FD	The incidence of tremor was significantly higher in dystonic patients as compared to controls (Rudzińska et al. 2013).	
BioStampRC, MC10 Inc		
HD	The average truncal Chorea Index was higher in individuals with HD than in controls. Individuals with HD walked less and took longer duration steps than the other groups. The UHDRS maximal truncal chorea score correlated with the average truncal Chorea Index (Dinesh et al., 2020).	Walk speed of individuals with HD showed a significant decrease over 12 months but not time spent lying, sitting, standing, and walking, truncal Chorea Index, step count and duration (Dinesh et al., 2020).

Individuals with HD spent over 50% of the total time lying down, more than individuals with prodromal HD, PD, and controls (**Adams et al., 2017**).

Cambridge Neurotechnology AW4 or Respironics Actiwatch 2 actigraph.

MPS Children with MPS III had significantly higher activity levels during the early morning hours compared to controls (**Mumford et al., 2015**).

CHDR Monitoring Remotely (CHDR MORE) platform

FSHD The classification between patients with FSHD and controls achieved 93% accuracy, 100% sensitivity, and 80% specificity. Features relating to smartphone acceleration, app use, location, physical activity, sleep, and call behaviour were the most salient features for the classification (**Maleki et al. 2022**)

Computational Motor Objective Rater

FD Head posture severity correlated with severity ratings from movement disorders neurologists using both the TWSTRS-2 and an adapted version of the Global Dystonia Rating Scale (**Zhang et al., 2022**)

DynaPort Move Monitor, McRoberts, The Hague, The Netherlands		
MG	Patients performed less VPA, spent more time sedentary, and engaged in less and shorter durations of MVPA than controls. Habitual physical activity correlated positively with 6 min walking distance (Birnbaum et al., 2021). PAL was lower in patients than in controls. No correlation was observed between disease severity and number of steps per day, nor between disease severity and PAL (O'Connor et al., 2019).	
EBIMU 9DOF		
FD	All parameters were validated by comparing with the TSWTRS-total score and the TWSTRS severity score. The magnitude of angular velocity parameters showed a higher correlation with clinical severity than rotation angle parameters (Park et al., 2019).	The ICCs were all more than 0.9 for the four parameters, which showed good agreement for all parameters (Park et al., 2019).
eMotion Faros 180		
ALS	Average daytime active, percentage of daytime active, total daytime activity score, total 24-hour activity score showed correlations with ALSFRS-R total and gross motor domain scores (Kelly et al., 2020).	All the activity endpoints investigated changed from baseline over the course of the study (48 weeks) to indicate a decline in physical activity over time (Kelly et al., 2020).

Fitbit One TM	
Pompe disease	Mean step count differed by age ($p < 0.01$), diagnostic delay ($p < 0.05$), disease duration ($p < 0.05$), and ambulatory status ($p < 0.05$). Patient-reported “fatigue and pain” score was inversely correlated with step count ($p < 0.05$) and peak 1-min activity ($p < 0.01$) (Hamed et al., 2019).
GaitUp Physilog 5, Lausanne, Switzerland	
FRDA	Controls were significantly more active than the FRDA group. Peak swing and stance period were the most discriminatory parameters. Correlation between the T25FW and the cadence was observed. Digitally derived stride width strongly reflected the risk of falling. Mean stride width from the real-world gait analysis dropped with GAA repeat length of the short allele (Mueller et al., 2021).
GENEActiv, Kimbolton, Cambs, United Kingdom	
HD	The developed system achieved 98.78% accuracy in discriminating between healthy and HD participants. MIS correlated with mULMS (Bennasar et al. 2018).

	HD participants had a greater percentage of walking bouts with irregular movements, lower walking consistency and higher across-bout variability compared to controls. UHDRS-TMS scores negatively correlated walking time and steps per day. Moderate correlations were observed between within-bout and across-bout gait consistency and the clinical measures of upper extremity chorea and total chorea (Keren et al., 2021).
DM1	A significant difference between the DM group and controls was detectable at each test. Stronger correlation values were observed between the 6MWT distance and ankle-worn accelerometry units. No correlations were identified in the DM1 group for wrist-worn devices (Jimenez-Moreno et al., 2019). High intra-accelerometer reliability ($p < 0.001$). There was no inter-accelerometer reliability between wrist-worn devices and ankle-worn (Jimenez-Moreno et al., 2019).
G-SensorVR, BTS Bioengineering, Italy	
FD	All the spatiotemporal parameters of the sub-phases of the TUG (turning, standing-up and sitting-down from a chair) had a significantly higher duration in cervical dystonia patients compared to controls (Celletti et al. 2021).

PWS	PWS exhibited significantly reduced values of HR in the antero-posterior and vertical directions compared with controls (Cimolin et al., 2020).
GT3X Actigraph, Manufacturing Technology, Inc. / GT9X	
HD	Physical activity was lower in patients compared to controls (Gil Polo et al., 2015).
Dermatomyositis	Patients with inactive disease had lower physical activity levels compared with controls (Berntsen et al., 2019). Sedentary time was positively correlated with disease duration and negatively correlated with VO₂ at respiratory compensation point and VO₂ peak. MVPA time was negatively associated with disease duration and the TUG score, and positively associated with time to respiratory compensation point, VO₂ at the respiratory compensation point, time to exhaustion, VO₂ peak, and current use of glucocorticoids (Pinto et al., 2016).

PWS	Youth with PWS spent 19.4% less time in weekly LPA and 29.8% less time in weekly VPA compared to controls (Castner et al., 2014). Physical activity across intensity categories differed between study groups. Amount of activity was lower in all patients than controls and in non-ambulatory than ambulatory patients and controls, but similar between ambulatory patients and controls (Arteaga et al., 2020). The PWS group displayed lower physical activity and higher sedentary time compared to the control group (Bellicha et al., 2020).	MVPA and walking capacity increased after the programme without significant effect on body composition (Bellicha et al., 2020).
DMD	The strongest relationships were observed between step activity and timed functional tests (particularly the 10-meter walk/run), with moderate correlations also observed with the 6MWD, knee extensor peak torque, and plantar flexor peak torque. Step activity moderately correlated with 10-meter walk/run test, RFF, 4SC. Patients who were still ambulatory after 2 years demonstrated baseline step activity nearly double that of those who were no longer walking 2 years later (Lott et al., 2021).	

	QMT and accelerometry measures had a moderate or strong correlations, particularly indexed arm QMT with total wrist vector magnitude, total indexed QMT with total wrist vector magnitude and indexed leg QMT with total ankle vector magnitude (Killian et al., 2020).	DMD participants also demonstrated a progressive decrease in physical activity at 1- and 2-years for wrist accelerometry and at 2-years for ankle accelerometry (Killian et al., 2020).	
ALS	Results were associated with ALSFRS-R. The variation in vertical axis showed the strongest correlation (van Eijk et al., 2019).	Less variability comparing with the ALSFRS-R (coefficient of variation 0.64-0.81 for inertial outcomes) (van Eijk et al., 2019).	Activity declined by 0.64%per month (van Eijk et al., 2019).
	The accelerometer models achieved a median multiclass AUC of 0.73 on 6 limb-related functions. The correlations across functions observed in self-reported ALSFRS-R scores were preserved in ML-derived scores (Vieira, 2022)		In the cohort of 54 test participants who received Edaravone as part of their usual care, the ML-derived scores were consistent with the self-reported ALSFRS-R scores. At the individual level, the continuous ML-derived score can capture gradual changes that are absent in the integer ALSFRS-R scores (Vieira, 2022)

Sarcoidosis	Daily physical activity and VO₂ max were lower in sarcoidosis patients than the predicted values in healthy age-matched individuals. Sedentary time was positively correlated with disease duration and negatively with VO₂ peak. MVPA was negatively associated with disease duration, and positively associated with VO₂ peak, and current use of corticoids (Pilzak et al., 2018).
Intelligent Device for Energy Expenditure and Activity (IDEEA), MinisunLLC, Fresno, CA	
CMT	Count of step climbing and sit to stand were lower in patients than in controls as well as mean daily step-climbing and walking velocities. Positive correlations were observed between strength of the knee extensor muscles and both count of steps climbed and sit to stand (Menotti et al., 2014).
Ipod	
HD	Amplitude of thoracic and pelvic trunk movements was significantly greater in participants with HD. Individuals with HD demonstrated rapid movements with varying

	amplitudes that continuously increased without stabilising (Kegelmeyer et al., 2017)	
Jamar Plus Digital, JLW Instruments		
DM1	Grip strength demonstrated strong correlations with self-reported inventories of upper (Hamel et al., 2022)	
JiBuEn gait analysis system		
SCA	There were significant differences in stride length, velocity, supporting-phase percentage, and swinging-phase percentage between the SCA group and the gait control group. A negative correlation was observed between velocity and ICARS and SARA scores. Correlations were observed between midsagittal relative vermis diameter and ICARS and SARA scores, as well as stride velocity variability (Jin et al., 2020).	
Kinesia motion sensor		
FD	Measures of head tremor are logarithmically related to Tremor Rating Assessment Scale (Elble et al., 2017).	Minimum detectable change (percent reduction) was approximately 66% of the baseline geometric mean. That is comparable to those previously reported for hand tremor (Elble et al., 2017).

LabVIEW2011, National Instruments, Ireland

HD	Step time CoV was greater in manifest HD than controls, as was stride length CoV for late HD. Phase plot analysis identified differences between manifest HD and controls for Step–Distance Balance, ratioΔ and Δangleβ. Disease burden score was significantly associated with ratioΔ, SDB. UHDRS-TMS was significantly associated with ratio Δ, SDB, Δangleβ and step time CoV, cadence CoV, stride length, and stride length CoV. RatioΔ produced the strongest correlation with UHDRS-TMS (Collett et al., 2014).	There was no significant difference between tests for any measure (ICCs: speed 0.94, step time 0.89, step time CoV 0.67, cadence 0.72, cadence CoV 0.59, stride length 0.83 and stride length CoV 0.57) (Collett et al., 2014).
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LEGSysTM, BioSensics, Newton, MA

SCA	Stride length variability, stride duration, cadence, stance phase, pelvis sway, and turn duration were different between SCA and controls. Sway and sway velocity of the ankle, hip, and centre of mass differentiated SCA and controls. Stride length variability, stride duration, cadence, stance phase, pelvis sway, turn duration, sway and sway velocity of the ankle, hip, and centre of mass showed moderate-to-strong correlation with SARA
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assessments of gait and stance and the BARS2
gait assessment (Zhou et al., 2021).

The cycle detection technique showed an accuracy of 97.6% in a Bland–Altman analysis and a 94% accuracy in predicting the severity of the finger-to-nose test. Among the extracted features, 22 showed an excellent correlation with finger-to-nose test and discriminated between SCA and control participants (Mohammadi-Ghazi et al. 2022).	The results showed excellent intra-rater reliability as the ICC was in the range of 0.94–0.99 (Mohammadi-Ghazi et al. 2022).
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Locometrix, Centaure Metrix, Evry, France

DM1 Patients displayed lower walking speed, stride frequency, stride length, gait regularity, and gait symmetry than controls. Strength of ankle plantar flexors, ankle dorsal flexors and neck flexors correlated with inter-stride regularity in the vertical direction. Knee extension strength correlated with gait symmetry in the anteroposterior direction. Centre of pressure velocity was greater in patients and correlated with neck flexion and ankle plantar flexion weakness and with inter-stride regularity in the vertical direction (Bachasson et al., 2016).

MetaMotionR, mbientlabs, San Francisco, CA

ALS Decreased stride length, increased stride duration and decreased walking speed were associated with lower functional walking scores, and the presence of a cane or walker (Geronimo et al., 2021).

Mimamori- Gait™ System LSI Medience, Tokyo, Japan

PSP Both PSP and PD patients shared the following similar hypokinetic gait characteristics: decreased velocity, step length, cadence and mean acceleration. Step time and variability in step time were mutually related. PSP patients showed characteristically low vertical

displacement and a higher acceleration than PD patients at the same cadence (**Hatanaka et al., 2016**).

Move 3 actigraphs, movisens GmbH, Karlsruhe, Germany

TSC Actigraph-measured movement was positively associated with ADHD and ASD symptoms. Higher ADHD symptoms and actigraph-measured movement levels were positively associated with ASD symptoms and negatively associated with IQ (**Earnest et al., 2020**).

MOX Accelerometry, Maastricht Instruments BV, Maastricht, the Netherlands

DMD Correlations with the PUL scale score were high for intensity and the total frequency of arm elevations per hour. Moderate correlations were observed between number of transfers per hour and PUL scale score from low-middle and from middle-high. High correlation was observed between the total number of transfers per hour and the PUL scale score (**van der Geest et al., 2020**).

Opal sensors, Mobility Lab, APDM, Portland, Oregon	
PSP	The Random Forest classifier allowed discrimination of PSP from PD with 86 % sensitivity and 90 % specificity, and PSP from healthy controls with 90 % sensitivity and 97 % specificity (De Vos et al., 2020). Control subjects were able to change their postural strategy, whilst PSP and PD subjects persisted in use of an ankle strategy in all conditions. PD subjects had root mean square values similar to control subjects even without changing postural strategy appropriately, whereas PSP subjects showed much larger root mean square values than controls, resulting in several falls during the most challenging sensory organisation test conditions (Baston et al., 2014). A simple linear regression model incorporating the three features with the clearest progression pattern was able to detect statistically significant progression 3 months in advance of the clinical scores (Sotirakis et al., 2022).

DMD	T-test results showed that, for all age groups, children of the same age with DMD and controls showed significant differences in RCC (An et al., 2020).	ICC of all groups exceeded 0.8 (An et al., 2020).
PWS	Children with Down syndrome and PWS exhibited reduced gait symmetry and higher accelerations at pelvis level than controls. While these accelerations are attenuated by about 40% at sternum level in controls and Down syndrome, PWS children display significant smaller attenuations meaning reduced gait stability. Significant correlations were observed between the estimated parameters and the GMFM-88 scale when considering the PWS group (Belluscio et al., 2019)	
ALS	The ability to extend the head backward and flex it laterally were the most compromised, with significantly lower angular velocity, reduced smoothness and greater presence of coupled movements with respect to controls (Pancani et al., 2017).	ICC was moderate to good in all movements and for most parameters (Pancani et al., 2017).

FSDH	For an average of 20.6 months, the iTUG duration stayed constant, whereas stride length, stride velocity, and trunk sagittal ROM changed, indicating poorer performance. Arm swing changed in a compensatory direction towards the normative mean (Statland et al., 2019).
	Gait parameters in FSDH participants were significantly altered compared with normative values. Stride velocity and trunk sagittal ROM had moderate to strong correlations to other FSDH disease measures (Huisinga et al., 2018). Reliability was excellent (ICC 0.84–0.99) (Huisinga et al., 2018).
HD	Gait speed, stride length, lateral step variability, and stride length variability were consistently observed to be significantly different between the HD and controls. HD participants demonstrated significantly greater dual-task cost for turning. Poorer performance on the SDMT and animal naming was significantly associated with increased gait variability. UHDRS-TMS were correlated with percent of time spent in swing phase, stride length CoV and percent of time spent in double support for all three conditions (Purcell et al., 2020).

Postural sway and control differed between patients with HD and patients with premanifest HD. Selected postural measures showed positive correlations with CAP scores and TMS (**Porciuncula et al., 2020**).

All measures of interest had good reliability (ICC: 0.764–0.887), except Total Power AP for patients with premanifest HD that had moderate reliability (ICC: 0.644) (**Porciuncula et al., 2020**).

Individuals with HD had greater APA acceleration amplitudes, smaller first step ROM and longer first step durations compared to controls. APA medial-lateral amplitude and duration under the no-load condition were significantly correlated. APA medial-lateral amplitudes under cognitive-load condition were significantly correlated with TFC and TMS. APA medial-lateral amplitudes under no-load condition were significantly correlated with TMS and SDMT. APA evaluation could predict gait speed (**Desai et al., 2021**).

90.5% of subjects were assigned to the right group after leave-one-subject-out cross validation and majority voting (**Mannini et al. 2016**).

Individuals with HD had a greater increase in standing postural sway compared to controls from single to dual-tasks and with changes to support surface. Patients with HD showed a greater dual-task motor cost compared to controls **(Muratory et al., 2021)**. Total sway, root mean square and mean velocity during sitting, as well as gait speed had the greatest importance in classifying disease status. Stepwise regression showed that root mean square during standing with feet apart significantly predicted clinical measure of chorea, and ordinal regression model showed that root mean square and total sway standing feet together significantly predicted clinical measure of tandem walking **(Desai et al. 2022)**.

FXS

FXS participants had reduced stride length and velocity, swing time, and peak turn velocity and greater double limb support time and number of steps to turn compared to controls under all conditions. Stride length variability was increased, and cadence was reduced in FXS participants in the fast-paced condition. There was greater dual-task cost on peak turn velocity in men with FXTAS compared to controls **(O'Keefe et al., 2021)**.

SCA

Larger variability of the swing period, toe-off angle and toe-out angle in pre-SCA2, and larger mean coronal and transverse ranges of motion of the trunk at the lumbar location and of the sagittal ROM of the trunk at the sternum location compared to controls. During tandem gait, pre-SCA2 subjects showed larger lumbar, trunk, and arm ranges of motion than controls. The toe-off angle and swing time variability were significantly correlated with the time to ataxia onset, whereas the toe-off angle and transverse ROM at trunk position during tandem gait were significantly associated with the SARA score (Velázquez-Pérez et al., 2021).

Increased gait variability was the most discriminative gait feature of SCA, toe-out angle variability (sensitivity = 0.871, specificity = 0.896) and double-support time variability (sensitivity = 0.834, specificity = 0.865) were the most sensitive and specific measures. These variability measures were also significantly correlated with the SARA and disease duration. The same gait measures discriminated gait of people with prodromal SCA from the gait of controls (Shah et al., 2021).

	LVC and outward acceleration but not general turning measures such as speed, allowed differentiating ataxic against healthy subjects in real life, with LVC also differentiating pre-ataxic against healthy subjects. LVC was highly correlated with SARA score, and activity-specific balance confidence scale (Thierfelder et al., 2022).	Moreover, LVC in real life allowed detecting significant longitudinal change in 1-year follow-up with high effect size (Thierfelder et al., 2022).
CMT	Five mean gait outcomes measured, four showed statistically significant changes over the 6-minute fast-as-possible walk: velocity, cadence, step time and trunk ROM. Stride length variability changed during the walking task, decreasing from bins 1–2, and remaining stable for bins 2–6. Changes in velocity, cadence, step time were related to general life satisfaction, but not perceived fatigue (Peterson et al., 2021).	

PAMSys-XTM sensors, BioSensics, Cambridge, MA

HD In the clinic, the SD of step time was increased in HD compared to controls. At home, significant differences were observed in seven additional gait measures (cadence, maximum step peak acceleration, maximum medial-lateral velocity, maximum medial-lateral displacement, average step peak acceleration, average medial-lateral velocity and displacement). The gait of individuals with higher TMS differed significantly from those with lower TMS on multiple measures at home (Andrzejewski et al., 2016).

Philips Respironics, Bend, OR

NP-C Significant correlations were observed among the bradykinesia metrics, indicating internal consistency. Measures of fine motor performance were significantly correlated with clinical disease severity, motor complications, and health-related quality of life, as assessed using the PDQ, UPDRS-IV, UPDRS, and AIMS. Dyskinesia metrics demonstrated significant associations with cognitive performance and attention, as measured by the NUCOG and NUCOG-A. In addition, disease duration was significantly

associated with tremor severity, as quantified
by the PTI (El-Masri et al. 2022).

Philips Respironics, Bend, OR

SBMA

Patients with higher AMAT
subscore increased total activity
count compared with controls
after intervention (Shrader et al.,
2015).

RehaGait, HAS-OMED, Magdeburg, German

HD

Device-extracted parameters
revealed significant improvement
in area, velocity, acceleration and
jerkiness of sway in cerebellar
repetitive transcranial magnetic
stimulation versus sham
stimulation (Pilotto et al., 2021).

SAM, Modus Health LLC, Washington, DC, USA

Rett syndrome

Repeatability of step-count pairs was excellent (ICC 0.91, 95%). The standard error of measurement was 6 steps/min, and we would be 95% confident that a change more than 17 steps/min would be greater than within-subject measurement error (Downs et al., 2015).

After intervention, the sedentary time was decreased. Positive effects with small to medium effect sizes were seen in sedentary time and that was maintained during follow-up period (Stahlhut et al., 2020).

SenseWear Armband, BodyMedia, Inc., Pittsburgh, PA, USA

Sarcoidosis

6MWD, SGRQ score, and SF-12 score showed strong associations with steps per day (Bahmer et al., 2018).

Scleroderma

Exercise capacity during daily activity was reduced compared with controls and was associated with early evidence of functional decay (Battaglia et al., 2017).

CMT	Results showed a decrease in daily steps taken in the CMT group, but shorter bouts of sedentary activity and more frequent transitions from sedentary to active behaviours compared to controls (Ramdharry et al., 2017).
SHIMMER sensors, Shimmer Research Ltd., Dublin, Ireland	
HD	Stride length and gait velocity were reduced, while stride and stance time were increased in patients with HD. Parameters reflecting gait variability were substantially altered in HD patients (stride length CoV and stride time CoV). Parameters representing gait variability (stride time CoV, stance time CoV, swing time CoV, stride length CoV, gait velocity CoV) showed moderate to strong correlations to UHDRS-TMS. Stride length and gait velocity showed moderate inverse correlations to UHDRS-TMS (Gaßner et al., 2020).
PSP	Gait speed was significantly reduced in patients with PD compared to controls and even more in atypical PD. Similar results were obtained for stride length. The maximum toe clearance and heel strike angle, toe off angles were significantly impaired in PD and atypical PD patients compared to controls but did not reveal a significant difference between both

	patient cohorts. Clinical ratings significantly correlated with gait speed and stride length (Raccagni et al., 2018).	
HSP	There were significant associations of absolute stride parameters with single SPRS items reflecting impaired mobility, with patients' quality of life, and notably with disease duration. Sensor-derived coefficients of variation, on the other hand, were associated with patient-reported fear of falling and cognitive impairment (Regensburger et al., 2022).	In a small 1-year follow-up analysis of patients with complicated HSP and fast progression, the absolute values of mobile gait parameters had significantly worsened compared with baseline (Regensburger et al., 2022).
Silmee™ Bar-type Light, Toshiba Corporation, Tokyo, Japan		
DMD	The Cj values had significant, strong to very strong correlations with the Brooke Upper Extremity Scale and the arm function scores for the DMD Functional Ability Self-Assessment Tool. The values also had a strong to very strong correlations with the elbow flexion strength (Fujii et al., 2019).	
Smartwatch		
HD	There was a significant correlation between the model chorea score and the patient-reported chorea score for the same assessment (Gordon et al., 2019).	

Step Watch™ Activity monitor (SAM), Cyma Inc. Seattle, USA

DMD	Significant correlations for 10-meter walk/run versus high and low stride rates were found at baseline. Changes in strides/day and percentages of high frequency and low frequency strides correlated significantly with changes in 10-meter walk/run speed (Fowler et al., 2018).	There were significant declines in average strides/day and percent strides at moderate, high and paediatric high rates as a function of age. Step activity outcomes were sensitive to change over 1 year, but the direction and parameter differed by age group (Fowler et al., 2018).
DMD	StepWatch accelerometer identified a decreased capacity for ambulation in boys with DMD compared to healthy controls. There were strong, significant correlations between 6MWD and all StepWatch parameters (Davidson et al., 2015).	
SCA	The objective monitor measurements were highly associated with disease duration and with the functional stage of disease. Monitor measurements were significantly correlated to SARA scores except for the percent of steps expended in moderate and high speeds of activity. Fewer monitor measures had significant correlations with walk and peg board scores (Subramony et al., 2012).	The objective SAM outputs also possessed high internal consistency, high ICC and could be fitted to a single factor by factor analysis (Subramony et al., 2012).

CMT	Minutes at low activity average, step at low and high activity averages, peak activity index average were correlated with myometer measures. High activity averages correlated with myometer measures and the Short Form 36 Physical Composite Score. Some Sustained Activity measures correlated with CMT Examination Score, myometer measures and Short Form 36 Physical Composite Score (Padua et al., 2016).	Test–retest for both the 6MWT and SAM demonstrated excellent reliability with a value >0.90 obtained comparing the two evaluations (Padua et al., 2016).	Statistical analysis showed a worsening of the StepWatch™ Activity Monitor outputs (Pazzaglia et al., 2019).
Roche HD Digital Monitoring			
HD	Good overall convergent validity of sensor-derived features to Unified HD Rating Scale outcomes and good overall known-groups validity among controls, premanifest, and manifest participants were observed (Lipsmeier et al. 2022).	All sensor-based features showed good to excellent test–retest reliability (ICC 0.89–0.98) (Lipsmeier et al. 2022)	

wGT3X-BT, Timik Medical, Herlev, Denmark

DM1 The individuals with DM1 were less physically active compared to healthy controls (Knak et al., 2020).

Table 2. Psychometric properties. *Abbreviations: Abnormal Involuntary Movement Scale (AIMS), Ataxia Instrumented Measures–Spoon (AIM-S), amyotrophic lateral sclerosis (ALS), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), anticipatory postural adjustment (APA), area under the curve (AUC), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), Brief Ataxia Rating Scale (BARS2), Box and Block Test (BBT), CAG–Age Product (CAP), Charcot-Marie-Tooth disease (CMT), coefficient of variation (CoV), Duchenne muscular dystrophy (DMD), electromyography (EMG), facioscapulohumeral dystrophy (FSHD), focal dystonia (FD), fragile X syndrome (FXS), Friedreich ataxia (FRDA), Gross Motor Function Measure (GMFM), harmonic ratio (HR), hereditary spastic paraplegia (HSP), Huntington disease (HD), intelligence quotient (IQ), International Cooperative Ataxia Rating Scale (ICARS), intraclass correlation coefficient (ICC), lateral velocity change (LVC), light physical activity (LPA), machine learning (ML), manual muscle testing (MMT), moderate physical activity (MPA), moderate-to-vigorous physical activity (MVPA), Modified Fatigue Impact Scale (MFIS), Motor Function Measure (MFM), mucopolysaccharidosis (MPS), myasthenia gravis (MG), myotonic dystrophy (DM), Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG), Niemann–Pick type C (NP-C), oxygen consumption (VO₂), Parkinson’s disease (PD), Performance of Upper Limb (PUL), physical activity level (PAL), Postural Tremor Index (PTI), Prader–Willi syndrome (PWS), progressive supranuclear palsy (PSP), quantitative muscle testing (QMT), rise from floor (RFF), range of motion (ROM), Scale for the Assessment and Rating of Ataxia (SARA), spinal and bulbar muscular atrophy (SBMA), spinal muscular atrophy (SMA), Spinocerebellar ataxia (SCA), Spastic Paraplegia Rating Scale (SPRS), St George’s Respiratory Questionnaire (SGRQ), standard deviation (SD), standard error of measurement (SEM), standardised response mean (SRM), stride length 95th centile (SL95C), stride velocity 95th centile (SV95C), Symbol Digit Modalities Test (SDMT), Timed 25 Foot Walk (T25FW), Timed Up and Go test (TUG), Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Total Functional Capacity (TFC), Total Motor Score (TMS), tuberous sclerosis complex (TSC), Unified Huntington’s Disease Rating Scale (UHDRS), Unified Parkinson’s Disease Rating Scale (UPDRS), vigorous physical activity (VPA).*

Spectrum of Pathological Conditions Assessed

Neuromuscular Disorders

Duchenne Muscular Dystrophy

Among the 18 studies that involved subjects with DMD, two studies also included subjects with Becker muscular dystrophy (Jacques et al., 2022) and Niemann–Pick type C (McErlane et al., 2021); the rest involved only subjects with DMD. One study showed that participants who were ambulatory two years after study initiation had almost double the level of step activity at baseline compared to subjects who were not ambulatory after two years (Lott et al., 2021). Two studies demonstrated that limb coordination (homolateral-limb coupling coefficient) and physical activity (stride count and time spent in different levels of activity) declined with age (An et al., 2020). Another study showed that total physical activity did not significantly change over one year (Jacques et al., 2022). Validity was demonstrated for numerous gait parameters (e.g., stride length, stride velocity) (Ganea et al., 2012). One outcome, SV95C which was qualified as a secondary outcome measure (Servais et al., 2022), was in public consultation for qualification as a primary endpoint until April 2023 and is very likely to be qualified in 2023. Of the two interventional studies identified, one, a randomised controlled trial, failed to show the effect of a nutritional supplement on steps or inactive minutes per day (Davidson et al., 2021), and the other showed that duration of walking episodes or the succession of walking episodes increased with prednisolone treatment (Jeannet et al., 2011). One research team used a smartphone maze game to evaluate and improve upper limb performance (Capelini et al., 2017). In another study, the feasibility of a patient-led initiative to assess upper and lower limb function through video analysis of four motor tasks was demonstrated (Ferrer-Mallol et al., 2022).

Amyotrophic Lateral Sclerosis

We found 15 studies that used various sensors, mainly inertial technologies, in the ALS population. One study showed an inverse association between overall acceleration average and ALS risk based on genome-wide association study and inertial data (Liao et al., 2022). Raw parameters as vector magnitude count and variation in vertical axis showed less variability than clinical assessment leading to a potential reduction of sample sizes by 30.3% for 12-month trials (van Eijk et al., 2019). Another study showed that daily home measurements such as step count, electrical impedance myography, and grip strength resulted in more accurate assessment to track progression and could reduce sample sizes for trials (Rutkove et al., 2020). Two studies used apps that integrated different tasks to monitor motor control in the upper body, speech, and cognition. One of these apps detected two metrics, error metrics and velocity rate, that are useful for inference of clinical variables (Agurto et al., 2019). Changes in typing activity (e.g., acceleration at key press, key release) were correlated with progression of dysfunction (Londral et al., 2016). Assessment of head movements through four parameters confirmed the efficacy of the Head Up collar by showing a significant improvement in the control of movement expressed as the median ratio of movement coupling value (Pancani et al., 2018). Another study showed that it is feasible to assess Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), a score that stratifies severity of ALS, remotely through an app (Meyer et al., 2022). Studies have also demonstrated that accelerometers and

electromyography can be used for evaluation of tremor frequency, involuntary movement (Vogelnik et al., 2022), and fasciculation (Crook-Rumsey et al., 2022).

Charcot-Marie-Tooth (CMT)

Six studies were found that used inertial sensors in subjects with CMT disease, four employed the sensors in the home setting. Four studies collected information on physical activity based on various variables (e.g., power of different activities, steps taken) without any ranking in terms of importance of these variables. One study attempted to characterise gait fatigability and demonstrated that velocity, cadence, trunk range of motion (ROM), step time, and stride length variability showed statistically significant differences during the 6MWT (Peterson et al., 2021). One study used the detection to tremor characteristics (e.g., frequency, spectral power) to study possible mechanisms for tremor (Saifee et al., 2015).

Myotonic Dystrophy Type 1 (DM1)

Four studies focused on difference between in the DM patients and controls mainly in terms of active minutes, limb accelerations, and gait abnormalities (i.e., walking speed, stride frequency, stride length). Three used inertial technology. The fourth showed the feasibility of remote video assessment of Timed Up and Go Test (TUG) and a digitally measured hand grip strength (Hamel et al., 2022).

Facioscapulohumeral Muscular Dystrophy (FSHD)

Four studies in subjects with FSHD focused on psychometric evaluation of outcome measures gained with inertial sensors. In one of them, data were acquired for six weeks through multiple technologies (accelerometer, apps, GPS, Google Places calls, microphone), and analyses resulted in an accurate classifier (Maleki et al., 2022).

Myasthenia Gravis (MG)

Two studies of subjects with MG continuously assessed for seven days, examined the validity of physical activity variables, defined as total (O'Connor et al., 2019) or levels of physical activity (e.g., low, moderate, high) (Birnbau et al., 2021).

Spinal Muscular Atrophy (SMA) Types 2 and 3

In a natural history study of subjects with SMA2 and SMA3, wrist angular velocity, wrist acceleration, wrist vertical acceleration, power, and percentage of active time were extracted from a magneto-inertial sensor worn at the wrist (Annoussamy et al., 2021). The reported results were similar to those described in DMD (Le Moing et al., 2016). In a limited number of ambulant patients, the device was placed on the lower limb and the SV95C, which was qualified in DMD (Servais et al., 2022) and studied in other dystrophies (Gidaro et al., 2022), remained stable over 12 months.

Spinal and Bulbar Muscular Atrophy (SBMA)

The single study of subjects with SBMA assessed the use of accelerometry to identify changes in the physical activity of patients after 10 days of functional exercises (Shrader et al., 2015).

Movement Disorders

Huntington Disease

Among the 26 studies on HD patients, 10 reported continuous (J. L. Adams et al., 2017; Andrzejewski et al., 2016; Dinesh et al., 2020; Gil Polo et al., 2015; Gordon et al., 2019; McLaren et al., 2021) or discontinuous (Cohen et al., 2018; Lang et al., 2021; Lipsmeier et al., 2022; Waddell et al., 2021) real-life assessments. Physical activity was assessed with different sets of variables in each study (e.g., activity profiles, step count, and time spent sitting). Contradictory results were obtained regarding discriminant validity of levels of physical activity (J. L. Adams et al., 2017; McLaren et al., 2021). Two studies found no difference in physical activity between patients and controls, but there were differences in spatiotemporal gait variables (Andrzejewski et al., 2016; Keren et al., 2021). Validity and accuracy of estimating gait events and various gait spatiotemporal parameters were assessed in controlled environments (Andrzejewski et al., 2016; Collett et al., 2014; Dalton et al., 2013; Desai et al., 2022; Gasner et al., 2020; Keren et al., 2021; Mannini et al., 2015; Purcell et al., 2020; Trojaniello et al., 2015) and in real-life settings in several studies (Andrzejewski et al., 2016; Dinesh et al., 2020; Keren et al., 2021; Lipsmeier et al., 2022). These studies used a selection of outcome measures (e.g., cadence, stride length, gait speed, variability) with no prioritisation of outcomes in terms of metric properties. In a cross-sectional study, compliance and psychometric properties of upper and lower limb variables (e.g., sway path, spiral drawing speed variability, median turn speed, and step frequency variance) were extracted from a digital monitoring platform (Lipsmeier et al., 2022). Balance and body sway (as root mean square (Desai et al., 2022; Muratori et al., 2021), jerk, sway area and power (Porciuncula et al., 2020), peak and mean thoracic and pelvic excursion (Kegelmeyer et al., 2017)) were impaired even at the premanifest stage of disease.

Upper limb function was evaluated in three studies in real-life settings using software to record speed of finger movement during computer typing (Lang et al., 2021), inertial technology to compute a chorea score, and a smartphone touchscreen sensor to assess the tap rate (Lang et al., 2021). One study demonstrated the validity of a model chorea score based on accelerometer data (Gordon et al., 2019). Three studies used ML approaches to extract composite scores (Bennasar et al., 2018) (i.e., movement impairment scores) as well as complex (Mannini et al., 2016) and standard (Gasner et al., 2020) spatiotemporal variables (e.g., stride length, velocity) for discriminant validity analysis. Use of ML based on inertial data, the accuracy of gait event detection (Mannini et al., 2015), the ability to predict upper limb impaired reaction (reaction time and error distance) (Lauraitis et al., 2018), and the potential of root mean square to serve as biomarkers of postural control impairments (Desai et al., 2022) were also demonstrated in a number of studies. Three studies demonstrated that compliance was good (Cohen et al., 2018; Shih et al., 2023) and reported that participants would be willing to wear the sensors again (J. L. Adams et al., 2017).

Progressive Supranuclear Palsy (PSP)

Seven studies focused on evaluation of subjects with PSP using inertial sensors in a clinical setting. Validity assessment via gait length or speed comparison between subjects with PSP and those with PD were not in agreement (Hatanaka et al., 2016; Raccagni et al., 2018). Patients with PSP have significant impairment in postural

control, expressed as root mean square, which can result in falls during challenging test conditions (Baston et al., 2014). Cerebellar repetitive transcranial magnetic stimulation had a significant effect on inertial parameters correlated with stability (i.e., area, velocity, velocity, acceleration, and jerk in the medio-lateral direction) compared to placebo (Pilotto et al., 2021). Upper limb assessment was restricted to the discriminant validity assessment of finger tapping-specific features (Djuric-Jovicic et al., 2016). Another study reported that a ML approach identified classifiers that discriminate PSP from PD with high sensitivity and specificity (De Vos et al., 2020). In the only longitudinal study of PSP subjects that we found, three out of 150 gait and postural features that were the most sensitive to change (i.e., mean toe off angle, mean turn velocity, standard deviation (SD) of stride length) were integrated in a regression model able to detect early progression (Sotirakis et al., 2022).

Focal Dystonia (FD)

We found nine studies regarding hand dystonia (Delrobaei et al., 2016; Nieuwhof et al., 2021; Panyakaew et al., 2020; Rudzińska et al., 2013) or cervical dystonia (Celletti et al., 2021; Elble et al., 2017; Mason et al., 2022; Park et al., 2019; Zhang et al., 2022). One study showed that instrumental detection of dystonic tremor outperforms clinical examination (Rudzińska et al., 2013). Two studies aimed to define the characteristics of dystonia (Delrobaei et al., 2016) and dystonia-associated tremor (Panyakaew et al., 2020) with multiple measures including force, power, and frequency. In the latter study, the authors built an accurate classifier (95.1%) that discriminated between essential tremor, dystonic tremor, and controls using two triaxial accelerometers and four pairs of surface EMG electrodes. One study used simultaneous MRI and accelerometer recording of tremor power to investigate its pathophysiology (Nieuwhof et al., 2021). In a single-participant interventional study, tremor magnitude assessed by 3D-kinematics was concordant with accelerometry and improved with deep brain stimulation (DBS) (Mason et al., 2022). Accelerations in three directions and speed measured with an inertial device during a TUG showed abnormalities in turning, standing up, and sitting (Celletti et al., 2021).

Genetic Syndromes with Manifestations of Ataxia

Spinocerebellar Ataxias (SCA)

We found nine studies in subjects with SCA that used inertial technologies. Evaluations in clinical settings demonstrated that wearable sensors are able to accurately capture gait parameters (i.e., mean step velocity, length, and swing and stance time)(Hickey et al., 2016) and turn (i.e., angle, duration, steps, mean velocity, lateral velocity change, outward acceleration, inward acceleration, average and maximum rate, and hesitations) (Shah et al., 2020; Thierfelder et al., 2022) in patients with SCA. Gait parameters and body sway measures (i.e., stride length, its variability, stride duration and speed, cadence, and swing, and stance time or percentage, double-support time variability, pelvis, ankle, and hip sway, turn duration, lateral velocity change, outward acceleration, and toe-out angle variability) consistently identified ataxic gait changes in the clinical setting (Hickey et al., 2016; Jin et al., 2020; Shah et al., 2021; Thierfelder et al., 2022; H. Zhou et al., 2022). Inertial technology also detected gait abnormalities as variability of the swing period, toe-off and toe-out angles, and elevation of feet at mid-swing as well as ranges of motion of the trunk and arm in patients with premanifest SCA type 2(Shah et al., 2021; Velázquez-Pérez et al., 2021).

Hereditary Spastic Paraplegia (HSP)

We found three studies led by the same team of researchers that studied subjects with HSP using inertial sensors fixed on the feet. Two of them, a pilot study and its validation (Martindale et al., 2017, 2018), validated a ML approach against a GAITRite system and manual sensor data labelling. The third study used the same approach on a large transversal cohort (n=112) and a small one-year longitudinal cohort (n=11)(Regensburger et al., 2022).

Fragile X Syndrome (FXS)

In two studies in patients with FXS, investigators performed an inertial detection of stride length and velocity, swing time, peak turn velocity, double limb support time, and number of steps to turn. A fast-paced gait exacerbated gait deficits, and stride velocity variability when gait was fast paced was significantly associated with the number of self-reported falls in the past year (O'Keefe et al., 2021). Further, cognitive performance was significantly associated with shorter stride length slower turn-to-sit times in premanifest patients (O'Keefe et al., 2018).

Friedreich's Ataxia (FRDA)

We found two studies of patients with FRDA that used inertial technology. Remote monitoring of several voice parameters, upper limb function through 14 parameters that can be grouped into parameters related to movement velocity, spectral frequency, and parameters related to deviation of the ideal trajectory, and 15 spatiotemporal gait parameters was feasible over one week (Mueller et al., 2021). The sensitivity of an upper limb composite score, the AIM-S, obtained through sensors contained in a spoon designed to detect deterioration in upper limb function, was greater than other measures (Corben et al., 2019).

Multisystemic Rheumatological Diseases

Five studies in subjects with sarcoidosis reported transversal evaluation of physical activity expressed in various way as number of steps (Bahmer et al., 2018; Cho et al., 2019; Chu et al., 2022; Pilzak et al., 2018), sit-to-stand transition (Cho et al., 2019), or acceleration per day (Korenromp et al., 2011) in real-life settings over seven to 14 days. Patient-reported physical activity and fatigue collected through an app correlated with smartphone-tracked physical activity (Chu et al., 2022). In dermatomyositis, three studies focused on real-life transversal physical activity assessment for seven to eight days. One study used vigorous physical activity (VPA) detection for the validation of the stage of exercise scale in several rheumatic diseases (Stephens et al., 2016). The single study on scleroderma, which used an accelerometer for a six-day period, explored validity of physical activity level detection (Battaglia et al., 2017).

Miscellaneous Diseases

Prader-Willi Syndrome (PWS)

Patients with PWS were included in eight different studies using accelerometers and/or gyroscopes. One study simply demonstrated significant agreement between mean stride length, mean stance percentage, and stance percentage coefficients of variation measured during two different walking tasks (Kraan et al., 2022). One study showed that because of the poor gait symmetry in PWS, upper body accelerations and the harmonic ratio (HR)

(i.e., measure of step-to-step symmetry based on trunk acceleration) can be used as innovative parameters for gait analysis, providing information that cannot be extracted from spatiotemporal parameters only (Cimolin et al., 2020). Two studies showed that patients with PWS do not meet healthy physical activity recommendations (Castner et al., 2014; Woods et al., 2018). Another group showed that moderate physical activity (MPA) accounts for the variability found in bone mineral content and density and its z-score (Duran et al., 2016). Two studies assessed the effect of training exercise programmes. One reported that training increases moderate-to-vigorous physical activity and walking capacity without effect on body composition (Bellicha et al., 2020), whereas the other found that training did not result in changes in moderate-to-vigorous physical activity but did cause improvements in body coordination, strength, and agility (Rubin et al., 2019).

Metabolic Diseases

One study, in subjects with Pompe disease, focused on concurrent validity of physical activity outcomes (step count and peak 1-min activity) (Hamed et al., 2019). Another study showed that measurements performed by patients at home with a handheld electrical impedance device did not differ significantly from those performed in the clinic setting. These measurements correlated with measures of muscle strength and function and quantitative muscle ultrasonography (Hobson-Webb et al., 2021). Two trials compared physical activity and rhythmicity of children with mucopolysaccharidosis (MPS) type III and Fabry disease to controls using continuous inertial recording (Mumford et al., 2015; Vallim J et al., 2019). One study of patients with GM2 gangliosidosis (GM2) used both a wearable device and a smartphone application and focused on compliance. This study failed to show significant changes in average daily maximum, average daily steps, or average daily steps per epoch over six months (Davies et al., 2020). We found one study that assessed the feasibility of the use of accelerometers on patients with Niemann–Pick type C, DMD, and with juvenile idiopathic arthritis using the same outcome measures as used in the study of patients with GM2 (McErlane et al., 2021). In another study, variables used in similar studies in PD (i.e., bradykinesia, dyskinesia, fluctuation score, percentage time immobile, and percent time with tremors) were used, demonstrating that bradykinesia and percentage time immobile are features of Niemann–Pick type C (El-Masri et al., 2022).

Rett Syndrome

Of the five studies found that reported studies of subjects with Rett syndrome, all but one were observational, and no study had controls. Four studies used the same three inertial devices (Downs et al., 2017; Stahlhut et al., 2017, 2020; Suresha et al., 2022), and one study compared these sensors (Downs et al., 2015). In a real-life setting, patients with Rett syndrome have sedentary behaviour based on a four-day accelerometer recording on the ankle (Downs et al., 2017). One study was interventional and assessed the effects of an interventional programme that aimed to increase enjoyable activities; positive effects on sedentary time, daily step count, and walking capacity were observed after the intervention (Stahlhut et al., 2020). Using ML algorithms and data derived from heart rate variability and activity metrics, a research team built an accurate classifier between high and low-severity Rett patients (Suresha et al., 2022).

Tuberous Sclerosis Complex (TSC)

We identified a single study in this patient population that used accelerometry to assess movement levels in controlled settings and correlated these with clinical parameters (Earnest et al., 2020).

Narcolepsy

Our review identified one study that compared energy expenditure and outcomes of physical activity (e.g., metabolic equivalent of task, step count, total energy expenditure), between a group of participants with narcolepsy type 1 and a group of participants with narcolepsy type 2 or idiopathic narcolepsy (Bornstein et al., 2021). A triaxial accelerometer was used, and there were no significant differences between the two groups that could account for weight gain.

IV. DISCUSSION

This review presents the developments in the field of digital outcome measures for a range of rare diseases with neurological manifestations. The increase in the number of studies on this topic attest of the growing interest in the field: In 2011, there were two published studies that included digital outcome measures, whereas in 2022 there were 25. A key finding of this review is that the use of digital outcome measures for motor function outside the clinical setting is feasible and it is being employed to evaluate subjects with a broad range of diseases. Although this is very encouraging, a publication bias cannot be excluded, as studies that failed to recruit participants or to collect robust data are less likely to be published.

An asset of technologies that provide digital measures of motor function is their potential application to the home setting, which is even more appealing since the COVID-19 pandemic. Although these devices are meant to be used at home, more than half of the evaluations in the studies took place in clinical setting. This indicates that many of these technologies are not yet ready to be used unsupervised. This could partially explain why the use of such outcomes for interventional studies remains uncommon (n=14) and limited to a small number of diseases (i.e., PWS, Rett syndrome, FSHD, DMD, SBMA, ALS, PSP, FD, and HD). Future research should focus only on sensors that are meant to be used outside clinical environment, unless there is a clear plan for technology evolution towards that goal or if the purpose of the device is not remote monitoring (e.g., a device aiming through digitalisation to remove part of the subjectivity of standard in-clinic assessments).

Another key finding is that most studies investigated a number of potential outcomes, mostly to demonstrate the validity of the technology via group comparisons and correlations with gold standard outcomes, whereas other psychometric properties were largely neglected. It is generally assumed that digital outcomes will be more sensitive to change in patient condition than standard tests and scales; however, this has yet to be proven, as suggested by the small number of studies reporting longitudinal data (n=34) or sensitivity to positive or negative change (n=21). A few research teams have performed psychometric evaluations, in CMT (Padua et al., 2016; Pazzaglia et al., 2019), ALS (van Eijk et al., 2019), FSHD (Gidaro et al., 2022), and FRDA (Corben et al., 2021), regarding the use of accelerometers for physical activity assessment, but the psychometric evaluations were not complete.

Despite the number of studies, we found that few outcome measures had been robustly studied and adopted as secondary or primary endpoints in clinical trials. An exception is the recent qualification of the SV95C in DMD (Goldsack et al., 2021). SV95C has been shown to be discriminative and to have concurrent validity, reliability, and clinical relevance as assessed through interview with patients, precise context of use, and sensitivity to positive and negative change. Normative data have been collected (Poleur et al., 2021). As stated on the FDA website (Food and Drug Administration, n.d.-a), the collection of information to formally qualified a clinical outcome assessment requires a long-term commitment. SV95C has been used in evaluation of subjects with limb-girdle muscular dystrophies, FSHD, and SMA, but how the qualification in DMD can be extended to less common diseases remains to be determined. This review did not identify other digital outcomes for which available metric properties description could complete the qualification process.

Outside diseases like DMD or Rett that are nearly only observed in males or female, respectively, very few studies paid specific attention to balance gender representation in the studied population, which may question the generalisability of the conclusion. Nevertheless, gender may clearly influence the phenotype of some autosomal condition such as SMA type 3. In this view, balancing the sample according to gender rather than to phenotype or phenotype/age can potentially result in a bias towards specific- and more specifically milder-phenotypes.

Of the 139 relevant papers, the vast majority used wearable sensors and fewer studies used portable sensors or non-wearable/portable technologies. The most common sensor is magneto-inertial technology (used in 126/139 studies). This technology is at a more mature stage than other types of sensors. As shown in Figure 2, most studies reported the use of sensors that were attached on the trunk or the back, which allow for gross evaluation of motor function and ambulation. In contrast, sensors fixed at the extremities allow for refined and more precise analysis of movement. Physical activity was the most frequently assessed parameter (n=58), followed by gait (n=39). This is likely because ambulation is critical from patient, caregiver and clinician perspectives. Technical reasons could also contribute as gait is easier to record digitally than movements that are more erratic. Development and validation of outcomes for upper limb are one step behind. Given the heterogeneity of variables, there appears to be no consensus on an efficient way to quantify upper limb motor function or activity. Quantification of abnormal movements such as tremor may be slightly easier to harmonise.

Although promising, ML approach was used in few studies; it was employed almost exclusively in studies of subjects with HD (Bennasar et al., 2018; Desai et al., 2022; Gasner et al., 2020; Lauraitis et al., 2018; Mannini et al., 2015, 2016). These studies demonstrated that ML algorithms can distinguish between normal and pathological motor performance. In rare diseases, ML faces the issue of the paucity of data. A major obstacle is the difficulty associated with gathering clinically valid information through interviews with patients, as the outcomes that result from ML are often non-intuitive. The solution resides in a clear association with a hard disease milestone or a clinically significant event, but this requires large amounts of data of high quality. Recent papers in DMD (Ricotti et al., 2023) and FRDA (Kadirvelu et al., 2023) showed the feasibility and the potential of ML, but these proof of mechanism study were conducted using different sensors in a controlled setting (Ricotti et al., 2023).

Although we used a pre-defined search strategy, our search had several limitations. Four papers from 2021 were not accessible in their full versions, and we had to discard them. Other limitations could be related to methodological reasons (e.g., we included only manuscript published in English, did not search grey literature, and only included references cited by selected papers). For this review, we excluded studies using technology-based devices with no potential to be used outside the hospital setting. Examples of excluded articles include studies using laboratory motion analysis such as hip kinetic and spatiotemporal gait parameters in boys with DMD (Heberer et al., 2016; Sienko et al., 2022) and Kinect-based stereo camera assessments that have been used in studies of subjects with ALS (de Bie et al., 2017) and FSHD (Han et al., 2015). Motion analysis is a robust alternative to standard clinical evaluation and has the potential to be used as a complementary approach to remote movement monitoring even at home setting.

V. KEY INSIGHTS

This review highlights several issues limiting the full integration of digital outcome measures into clinical trials and practice. Despite promising initiatives, most studies included in this review are monocentric, and almost all studies were performed in small cohorts. It is also difficult to compare or pool the data between studies, as methodologies were very diverse and as different manufacturers provide different algorithms to analyse the recorded data.

Future research should focus on the systematic validation leading to the qualification of devices, variables, and algorithms to allow remote evaluation of diseases. To address the issue of generalisability, open-source platforms that facilitate data collection, sharing, and interpretation are necessary. The qualification of a first digital outcome could pave the way to development of digital outcome measures.

FOCUS ON RARE REAL-WORLD WALKING SPEED

The information presented in this section is derived from a published systematic literature review entitled “Real world walking speed as an outcome measure for clinical trials – a systematic review, regulatory status and future directions” by M. Poleur et al., accepted for publication in *Frontiers in Digital Health*. This article is not reproduced in its entirety.

I. INTRODUCTION

Walking ability is a key determinant of quality of life as it is essential for many activities of daily living (Park and Kim, 2019) and to maintain independence (Mirelman et al., 2018). Because walking relies on multiple physiological systems, gait assessment has become a central component of clinical evaluation in neurological (Fischer et al., 1999; McDonald et al., 2013), cardiovascular, pulmonary (Crapo et al., 2002) diseases.

It can be characterised by qualitative, functional gait parameters (i.e. speed, stride length) and quantitative, activity-based gait parameters (i.e. stride per hour, walking distance). Among these parameters, walking speed has been associated with disease severity, prognosis, and functional status across numerous diseases including MS, heart failure, and stroke (Shulman et al., 2008; Fuentes-Abolafio et al., 2020; Tasseel-Ponche et al., 2022). Also in healthy elderly patients, slower walking speed could predict a higher risk of mortality (Rosmaninho et al., 2021; Liu et al., 2024) and dementia (Hackett et al., 2018). Walking speed has been extensively used as a meaningful outcome measure in clinical trials, particularly within neurological research (van Munster and Uitdehaag, 2017; Kishnani et al., 2023).

Walking tests are currently conducted in controlled environments and therefore susceptible to contextual biases. Among them, the Hawthorne effect, defined as a change in behaviour as a response to observation and assessment (Jeon et al., 2023). This awareness may lead participants to intentionally or unintentionally alter their performance. For example, some individuals might walk faster than usual to appear more capable, while others might deliberately walk more slowly if they know that reduced walking speed increases their eligibility for an appealing clinical trial. Moreover, such tests provide only a limited snapshot of a patient's walking ability, potentially influenced by transient factors like mood, fatigue, or stress. These biases potentially result in false-positive or false-negative trial outcomes.

Although real-world monitoring with wearable sensors may initially influence patient behaviour due to awareness of being monitored, an effect that is deliberately leveraged by many commercial activity trackers to encourage increased step-based performance, continuous data collection over extended periods (e.g., several weeks to months) substantially mitigates this influence. Over time, initial behavioural modifications are expected to stabilise

into habitual patterns that more accurately reflect the patient's true functional performance in daily life, thereby providing a reliable measure of real-world walking speed that is robust to transient behavioural changes. Despite this promise, most diseases still lack consensus on which digital mobility variables best capture the clinical picture and sensitively detect meaningful change. Recent reviews highlight many small initiatives in various fields but only few reports of robust validated outcomes (Moreau et al., 2023a; Poleur et al., 2023; Woelfle et al., 2023). These reviews describe a wide range of commonly used sensor modalities, including IMUs composed of accelerometers and gyroscopes, pressure sensors, surface electromyography, and instrumented insoles, as well as their diverse body placements. Typical sensor locations include the wrist, ankle or foot, and lumbar region, selected according to the functional domain and disease being monitored. These sensors have shown promise in detecting subtle changes (Woelfle et al., 2023) or fluctuations motor performance (Moreau et al., 2023) with greater sensitivity than conventional clinical assessments. Previously mentioned reviews emphasised the need for further validation of digital outcomes, yet none identifies outcomes or devices that have received regulatory approval or undergone any form of qualification.

Regulatory qualification is a critical step to integrate digital outcomes into evidence-based medicine. It ensures their acceptability for use in clinical trials and healthcare decision-making (Bakker et al., 2025). Without regulatory qualification, digital outcomes may be considered exploratory and not suitable as primary or secondary endpoints in regulatory trials. This limits their use in drug development, labelling claims, and ultimately their impact on patient care. Moreover, the qualification process promotes standardisation, facilitates study comparisons, and integrates findings into both clinical practice and research.

This review synthesises current knowledge on the use of real-world walking speed as an outcome measure for patient evaluation. It also emphasises digital outcomes and wearable health technologies that have or seek to achieve regulatory qualification from agencies such as the FDA and the EMA. Additionally, we aim to identify and discuss the main challenges in the translation of real-world walking speed metrics into regulatory-qualified clinical outcomes.

II. METHODS

Data Selection

First, we completed a systematic review. The search strategy is explained in our published protocol, available at the International Prospective Register of Systematic Reviews (Registration: CRD42025633578) and adhered to the PRISMA (Liberati et al., 2009).

To achieve our objective of identifying methods that are in the advanced stages of the regulatory approval process, we chose to focus on final peer-reviewed papers accessible through MEDLINE and EMBASE. Subsequently, we conducted a review of the literature using a comprehensive search with pre-defined selection criteria and search strategy.

This approach allows us to systematically review the most current, high-quality evidence, particularly those studies that represent advanced stages of development – whether through late-phase clinical trials or post-marketing studies. We searched MEDLINE via Ovid on August 1, 2024, and EMBASE on December 15, 2025. The MEDLINE search was updated on the same day. We included English-language studies published from 2019 onward. As English is the predominant language of regulatory and scientific communication, relevant evidence intended to support regulatory approval is expected to be available in English. The search was limited to the most recent years to reflect the current regulatory landscape and contemporary evidentiary standards. In medical device development, regulatory efforts that have not progressed within this timeframe are unlikely to succeed without substantial new evidence or technological modification; consequently, older unsupported studies have limited relevance for assessing present-day regulatory feasibility.

Eligibility Criteria

Eligibility of records was assessed using the PICO framework to define inclusion and exclusion criteria based on the four key components: Population, Intervention, Comparison, and Outcome, and the additional criteria of Type of Study, Language of Publication, and Publication Date (Table 3).

Criteria	Inclusion	Exclusion
Population	Large human population	Studies on small populations (30 patients) except if the study is linked to a substantial body of evidence supporting the validity of the device or digital outcome measure (i.e., other study, information on regulatory agency websites) Studies on healthy population except if the study is linked to a substantial body of evidence supporting the validity of the device or digital outcome measure Studies on animals
Intervention	Use of digital technology to assess real-world walking speed	Studies in controlled environment Studies that use technology for intervention rather than for monitoring
Comparison	Not applicable	Not applicable
Outcome	Studies focusing on full psychometric evaluation and targeting validation of digital outcome or device.	Studies with a low level of validation (such as those reporting only partial or incomplete psychometric evaluation) should be considered only if supported by a substantial body of evidence (i.e., other study, information on regulatory agency websites) demonstrating the validity of the device or digital outcome measure used
Record type	Qualitative, quantitative and mixed-method studies, systematic reviews, opinion pieces, theoretical papers without primary data	Conference abstract and study protocol
Other	Language of publication English Studies published between January 2013 – April 2023 Studies available in full-text format	Publication not available in full text

Table 3. Eligibility criteria.

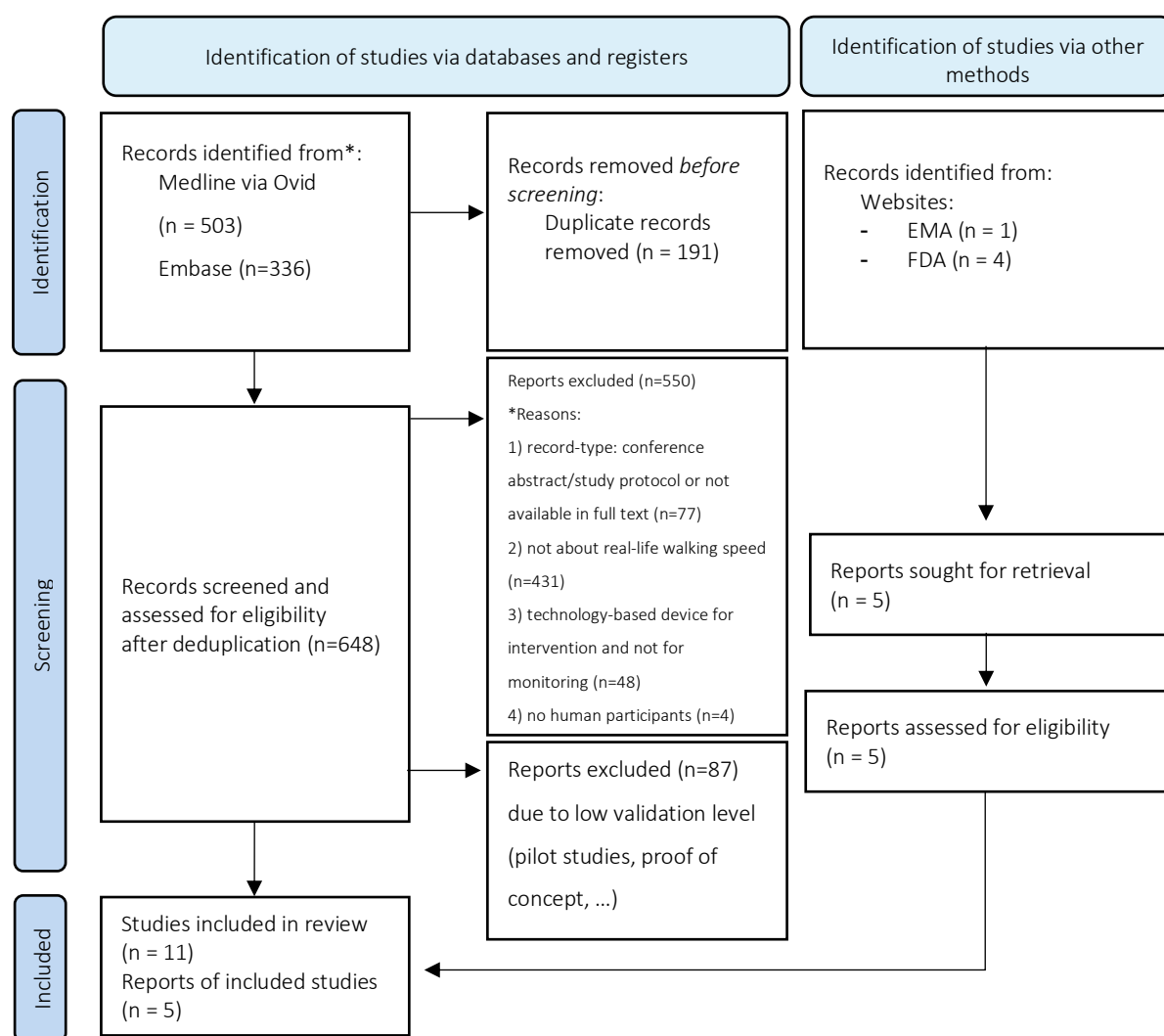


Figure 4. Flow chart of the selection process. Abbreviations: European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA).

Study Selection and Data Extraction

After running the search strategy, citations of all the selected papers were uploaded into Covidence, a software platform designed to conduct systematic reviews. Duplicates were manually eliminated. MP and CT independently screened titles and abstracts and subsequently full texts for eligibility. Disagreements were resolved by a third reviewer (LS). We included reports that assessed real-life walking speed in humans. After this initial screening, the full texts of all remaining reports were examined in a second round of review. During this stage, studies reporting proof-of-concept or pilot data were excluded unless they could be clearly linked to a broader body of evidence supporting a given outcome or device. Such evidence could consist either of external supporting material, including information available in regulatory sources (e.g., qualification reports, regulatory submissions), or of multiple related studies which, when considered together, constituted a sufficiently large and coherent body of

evidence. No restriction was applied regarding gender, age or ethnicity. The two reviewers compared their findings, and potential disagreements were resolved by consensus or with the help of a third reviewer (LS).

Device and outcome characteristics were extracted from all data collected (outcome, targeted population/context of use, broader initiative, technology, number and location of sensors). Two assessors (MP and CT) extracted these data in Covidence. Results from both extractions were compared until assessors reached consensus.

The main outcomes reported in these studies, including validity, reliability, feasibility, accuracy, and sensitivity to change, were also extracted. In addition, information on the minimal clinically important difference (MCID) was gathered. The MCID represents the smallest change in a measurement that is perceived as beneficial or meaningful by patients or clinicians, was also collected. This parameter is particularly important because it helps to determine whether observed changes are not only statistically significant but also clinically relevant.

Additional Data

We collected additional data to ensure that no crucial information was overlooked by our systematic methodology. As a second approach, to find research results that have regulatory visibility, we searched the websites of regulatory agencies. We focused on the FDA and the EMA as these regulatory agencies are the most influential worldwide. Their expertise in the approval and regulation of medicines and medical devices make them well-positioned to provide an overview of the cutting-edge biomarkers. We considered initiatives that have demonstrated an intention to seek formal approval, as evidenced by the submission of a Letter of Intent (LOI) – a formal document submitted to a regulatory authority to communicate the intent to engage in a regulatory process (e.g., for drug or device development).

We also directly contacted members of these agencies to collect additional relevant evidence. Based on the findings of the literature research we searched Medline and Clinicaltrial.gov database on December 1st, 2024, for ongoing studies linked to the identified and selected reports.

Data Analysis and Synthesis

Data were synthesised using a narrative approach, given the heterogeneity in study designs, populations, and outcomes across the included papers. To facilitate comparison and highlight condition-specific findings, studies were grouped according to the disease or disorder they addressed. Within each group, we examined common themes, key outcomes, and methodological characteristics, providing a structured summary of the evidence for each condition.

III. RESULTS

Source of the Data

Regulatory Agencies Web Site and Contact

There is no outcome or device that has been validated by the FDA for the assessment of walking speed in real-life. We found 4 letters of intent on the FDA website (Food and Drug Administration, n.d.-c) regarding our concept of interest. One of them applies for the use of Biostamp® in HD and it was declined by the FDA in 2020. Two LOI were accepted regarding the use of actibelt® in MS and sarcopenia respectively. The use of Actimyo® in DMD was proposed and accepted in the most recent LOI.

Only one outcome or device was identified as regulatory approved in the EU. The EMA website published the complete qualification package (European Medicines Agency, n.d.-c.) of the SV95C as primary endpoint in superiority studies for ambulant patients with DMD above 4 years old (Servais et al., 2023, 2024).

There is at least one device in the regulatory pathway in the EU with a focus on real-world walking speed. The FDA website published a briefing (European Medicines Agency, n.d.-d) that asks for EMA scientific advice on the usage of changes of real-world walking speed as measured with actibelt® technology as phase III endpoint for MS, recovery after surgical treatment of hip fracture and sarcopenia. The EMA's unpublished scientific advice, which included the key questions to be addressed, was shared with the applicants in 2017, prior to the publication of the €50 million Innovative Medicines Initiative (IMI) call (Innovative Medicines Initiative, n.d.).

Literature Review

A flow chart of the process used for inclusion of clinical studies in our analysis is shown in Figure 4. Our literature search identified 648 records. Of these, 550 were excluded as they did not meet the scope of the review. An additional 87 studies were excluded because they consisted of small pilot studies or proof-of-concept reports without sufficient relevance for validation purposes. Information on collected data are summarised in table 4 and 5. All papers except one were part of broad initiatives, namely the qualification of the SV95C and Mobilise-D consortium (MOBILISE-D). The last paper is linked to the LOI submit to the FDA for the use of actibelt® in sarcopenia.

Clinical Trial Database

We identified one and 14 ongoing studies related to the MOBILISE-D initiative and SV95C qualification, respectively.

Broader initiative	Author and year of publication	Disease	Number, age and sex of participants (F/M, age $\pm$ SD [range])	Device name	Technology used	Outcome	Number/ location of sensor(s)	Context of use
In collaboration with MOBILISE-D	Kirk, C. et al. 2023	PD	88 PD, 111 controls	AX3 (Aivity, United Kingdom)	Triaxial accelerometer	RWS	1 sensor (lower back)	Participants underwent clinical and real-world assessments at 18, 36, 54, and 72 months following the baseline assessment. Participants wore the device for 7 days
MOBILISE-D	Kirk C., et al. 2024	CHF, COPD, healthy adults, MS, PD, and PFF	97 participants: 17 controls (72.35 $\pm$ 6.00 y.o.), 9 CHF (68.00 $\pm$ 12.80 y.o.), 17 COPD (69.35 $\pm$ 9.10 y.o.), 13 MS (47.23 $\pm$ 11.09 y.o.), 15 PD (69.20 $\pm$ 7.48 y.o.), 11 PFF (79.70 $\pm$ 6.86 y.o.)	Dynaport MM+ (McRoberts)	Triaxial accelerometer, triaxial gyroscope	RWS	1 sensor (lower back)	Participants were monitored in the laboratory (INDIP reference system) and the real world (2.5 h). Participants were also asked to wear Dynaport and a multisensor INDIP reference system
MOBILISE-D	Boehme P., et al. 2019	Frailty, heart and lung diseases, neurologic and neuro-degenerative diseases, cancer	N/A	N/A	Wearables + smartphone applications	RWS		
SV95C qualification	Lilien C., et al. 2019	DMD, type 3 SMA	23 ambulant participants	ActiMyo (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	Digital 6MWD	2 sensors (wrist and an ankle or on both ankles)	Participants performed a 6MWT wearing the device. Some patients performed a second test 6 months later

SV95C qualification	Poleur M., et al. 2021	Healthy subjects	91 controls (41/50, 16.9 ± 16 y.o.)	ActiMyo (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	SL50C, SL95C, SV50C, and SV95C	2 sensors (dominant wrist and ankle)	The sensors were worn for 1 month at baseline and at 12 months
SV95C qualification	Gidaro T., et al. 2022	FSHD and LGMDR2	18 participants: 8 FSHD and 10 LGMDR2	ActiMyo (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	SL50C, SL95C, SV50C, and SV95C, total number of strides, walked distance	2 sensors (dominant wrist and ankle)	Patients presented here were included in the ATYR1940-C-004 study (NCT02579239), in which digital outcomes were included as exploratory endpoints. The ATYR1940-C-004 study was a phase 1b/2, multicentre, open- label, intra-patient dose-escalation study evaluating the safety, tolerability, immunogenicity, and biological activity of ATYR1940, a histidine aminoacyl tRNA synthetase promoting skeletal muscle homeostasis and resetting the immune system to control or reduce tissue damage. They wore the DHT continuously from screening to the end of the trial (4 months)
SV95C qualification	Servais L., et al. 2022	DMD	Unknown	Syde (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	SV95C	2 sensors (wrist and ankle)	Patients with DMD were recorded for 1 month at baseline and at 6 months

SV95C qualification	Servais, L. et al. 2021	DMD	Various DMD cohorts	ActiMyo (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	SV95C	2 sensors (dominant wrist and ankle)	To assess accuracy, the 6MWT was assessed simultaneously using the wearable device/system and the classical method for 31 tests performed in 23 patients in a broad range of clinical conditions. To assess reliability, they studied the relationship between the recording period averaging and the variability of the measure by tracing the variance in 28 patients tested in a non-controlled setting. The relationship between stride velocity, stride length, and distance per hour and the 6MWT, NSAA and 4SC was assessed in 45 DMD patients. The sensitivity to change was assessed on 6 months in 31 patients and on a subgroup of 20 patients older than 6 y.o. and walking <450 m in the 6MWT.
SV95C qualification	Haberkamp M., et al. 2019	DMD	Boys (8.3 ± 2.1 [5–14] y.o.)	ActiMyo (Sysnav, France)	Triaxial accelerometer, gyroscope, magnetometer, and barometer	SV95C, SV50C, SL95C, SL50C, and the distance walked per recorded hour	2 sensors	Home-based environment, 1-month recording

FDA	LOI	Mueller A., et al. 2019	Sarcopenia	26	slow-walking	elderly	actibelt	Triaxial	Several gait	1 sensor (waist)	During the validation study, the subjects
regarding the				subjects	(15/11),	217	RCT2 (Trium	accelerometer	parameters		completed a course, at least twice,
use	of			patients	with sarcopenia		Analysis				through the clinic that was designed to
actibelt	in			(126/91,	79 ± 5.45 y.o.)		Online,				simulate a real-world environment.
Sarcopenia							Germany)				Patients were monitored over 25 weeks
											during a phase 2b interventional clinical
											trial, both during and between visits.
											Patients were instructed to wear the
											device continuously for a minimum
											period of 5 days before each planned
											clinical site visit.

Table 4. Characteristics of included studies. Abbreviations: 4-stair climb (4SC), 6-minute walk distance (6MWD), 6-minute walking test (6MWT), Axivity accelerometer (AX3), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), digital health technology (DHT), Duchenne muscular dystrophy (DMD), U.S. Food and Drug Administration (FDA), facioscapulohumeral dystrophy (FSHD), Inertial Device for In-Patient reference system (INDIP), limb-girdle muscular dystrophy type R2 (LGMDR2), Letter of Intent (LOI), Mobilise-D consortium (MOBILISE-D), multiple sclerosis (MS), not available (N/A), North Star Ambulatory Assessment (NSAA), Parkinson's disease (PD), proximal femoral fracture (PFF), randomised controlled trial (RCT), real-world walking speed (RWS), standard deviation (SD), stride length 50th centile (SL50C), stride length 95th centile (SL95C), spinal muscular atrophy (SMA), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C).

Broader initiative	Author and year of publication	Feasibility/Compliance	Accuracy	Reliability	Clinical validity	Sensitivity to change	MCID	Other
MOBILISE-D	Kirk, C. et al. 2023				RWS was significantly different between PD and controls at each time point and WBs. At 36 months, there was no significant association between MDS-UPDRS III score and RWS at all WBs. There was a significant negative association with the MDS-UPDRS III at WBs between 30 and 60 seconds ($p = 0.047$). There was no association between changes in RWS and changes in MDS-UPDRS III at all WBs and any other WB duration threshold.	RWS significantly slowed in PD by 2 cm/s per year ($p = 0.014$) and in controls by 1 cm/s per year ($p \leq 0.001$), when aggregated within WBs >10 seconds. RWS calculated within each WB threshold slowed significantly at each WB duration, excluding long WBs (>60 seconds) in PD. The rate of decline in RWS was larger in PD in comparison with controls at each WB duration threshold, excluding WBs >60 seconds where no difference was observed compared with controls.		

MOBILISE-D	Kirk C., et al. 2024	In controlled environment, the MAE and MRE for walking speed estimation ranged from 0.06 to 0.12 m/s and -2.1 to 14.4%. Real-world MAE ranged from 0.09 to 0.13 m/s and mean absolute relative error from 1.3 to 22.7%. Lower errors were observed for cohorts without major gait impairments, less complex tasks, and longer WBs. ICC ranged from 0.79 to 0.91 in controlled environment and 0.57 to 0.88 in unsupervised environment
MOBILISE-D	Boehme P., et al. 2019	

SV95C qualification	Lilien C., et al. 2019	In 2012, the device was used in a clinical study for controlled and home-based monitoring of upper-limb movements in non-ambulant DMD patients (NCT01611597), which demonstrated the autonomy and feasibility of device use. Patient compliance tended to decrease over time.	The difference between the distance measured by the inertial device and the reference 6MWT (after correction for the length of the turns around the cones) was within 5%	The validated 6MWT and the NSAA have been correlated with the device's variables.
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SV95C qualification	Poleur M., et al. 2021	Among the 91 healthy controls who wore the wearable device for one month, 90% recorded more than 50 h, and 77% recorded more than 180h at baseline. During the second period, 86% recorded more than 50h, and 73% recorded more than 180h. The main reason reported by subjects who recorded less than 50h was technical issues.	In comparison to ambulant DMD patients of the same age, healthy children present a 67.3% higher SV95C. The difference for other variables was not as extreme, and there is some overlap between DMD and control participants (SL50C 31.39%, SL95C 52.41%, SV50C 25.72%, distance walked per hour 63.13%) 6MWD was significantly correlated with SV50C, SV95C, and SL95C in the younger group. In the adult group, 6MWD was only correlated with 'maximum performance' measures SV95C and	In the younger group, only SL50C increased after one year. We did not observe a significant change after a year in adults in stride length and velocity.
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					SL95C. Among the group aged 5 to 17 y.o., height was highly correlated with age, 6MWD, 10MWT, SV50C, SL50C, and weakly correlated with SV95C and SL95C. In adults, height was only correlated with SL50C and SL95C.
SV95C qualification	Gidaro T., et al. 2022	18 patients enrolled in the study, 10 were ambulant and compliant with wearable sensor analysis, 3 patients were not sufficiently compliant (less than 22 days of data), 3 patients were non-ambulatory, 2 patients were not given the sensor.	All the measurements showed high reliability according to ICC values (all >0.9). SL50C, SL95C, SV50C, and SV95C showed lower SEMs (all <0.03) compared to total number of strides and walking distance (40.2 and 28.5).	Median speed, length, SV95C and SL95C were significantly different at baseline between subjects with FSHD and LGMDR2. Median speed (R=0.842), median length (R=0.866), SV95C (R=0.866) and SL95C (R=0.915) strongly correlated with MMT.	Slight decreases in all variables were observed in subjects over time with significant decreases ($p \leq 0.05$) for median speed, SV95C and SL95C.

SV95C qualification	Servais L., et al. 2022	A total of 180 hours was optimal, with good compliance and low measurement variability; 90% of patients recorded 180 hours over 1 month.	ActiMyo stride detection is derived from the 3D trajectory of the ankle, providing a 98% stride detection success rate over 2000 atypical strides, including small steps or sidesteps. In healthy volunteers, ambulation parameters were captured with similar levels of accuracy to motion capture, with a peak-to-peak discrepancy rate below 2.5%	SV95C had moderate but significant correlations with the 6MWT and NSAA	After 6 months, in patients ≥ 7 y.o. with baseline 6MWT below 450 m, SL95C declined by 2.4% ($p < 0.05$), SV50C by 4.7% ($p < 0.05$), and SV95C by 8.5% ($p < 0.01$). SV95C is sensitive to the positive functional changes associated with steroid treatment; in steroid-naïve patients, steroid initiation resulted in an 11.6% increase in SV95C after 6 months, while age-matched patients receiving stable steroid treatment experienced a 6.8% decline.	The MCID for SV95C was calculated using the distribution-based methods described by McDonald et al. as 0.1 m/s (a relative 6.24% decline), corresponding to a 36 m difference in 6MWT (30 m is the accepted 6MWT MCID in DMD trials).	Large sample sizes are required for studies employing the 6MWT as a primary endpoint. In the phase III ataluren study for DMD, an estimated 105 patients per treatment arm were needed to show a 30 m difference in 6MWT at 48 weeks with 85% power [31]. For SV95C, 14 patients per arm with DMD aged 7 y.o. or above (with 6MWT baseline < 450 m) provide
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sufficient
statistical power
(80%) to
demonstrate
significant
stabilisation of
motor function
with treatment
at 6 months

SV95C qualification	Servais, L. et al. 2021	The difference between the distance measured during the 6MWT using the wearable device and the corrected reference was within 5%.	They showed good stability with low variability from 2.22 up to 4.41% for the SL95C and SV95C, respectively, for 180h of wearable device use.	Analysis showed a good correlation of SL95C and SV95C with the baseline 6MWT (0.68 and 0.54, respectively) and with NSAA (0.78 and 0.64, respectively).	They observed a significant decline in SL95C (2.4%), SV50C (4.7%), and SV95C (8.5%) over 6 months for patients aged ≥ 6 y.o. with a baseline 6MWD below 450 m.
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SV95C qualification	Haberkamp M., et al. 2019	The SV95C was calculated from a period of 180 h of summed recorded data per individual. This period seemed to ensure low variability while keeping good compliance. Daily recording including weekends is needed to obtain representative data. Therefore, in ambulant DMD patients, 30-day wearing periods are proposed to ensure that sufficient data are generated during a set period for almost all patients.	The distance measured from reconstruction of foot trajectory of ambulant patients as assessed by the magneto-inertial sensor corresponds to the real distance as measured manually. Accuracy of measurements using the device was assessed by comparison with an optical motion capture system in healthy subjects.	SV95C was significantly correlated with the validated 6MWT and NSAA. Baseline normative data indicate that stride speed and stride length clearly discriminate between controls and DMD, especially when expressed as the 95th centile.	Longitudinal analyses showed that changes in SV95C at 6 months (31 patients) and 12 months (11 patients) were consistent with those observed for the 6MWT in DMD studies.	MCID of 0.1 m/s for SV95C
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FDA regarding the use of actibelt in Sarcopenia	LOI	Mueller A., et al. 2019	Ultimately, patient-days accelerometry data were collected from 192 patients and 32 sites. This demonstrates the feasibility of continuous monitoring in global clinical trial settings including elderly populations. We observed that patient compliance patterns were highly variable, with some patients greatly exceeding the requested wear time and others contributing far less	9668 of slow-walking adults with a residual standard error of 0.08 m per second in the independent validation study and 0.08, 0.09, and 0.07 m per second for the 4mWT, 6MWT, and 400mWT, respectively.	In-clinic measurement of gait speed in frail adults with a residual standard error of 0.08 m per second in the independent validation study and 0.08, 0.09, and 0.07 m per second for the 4mWT, 6MWT, and 400mWT, respectively.	They found positive associations between the short 4mWT gait speed assessment and gait speed in bouts between 5 and 20 steps (correlation coefficient of 0.23) and longer 6MWT and 400mWT assessments with bouts of 80 to 640 steps.
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Table 5. Psychometric properties and validation evidence for real-world walking speed measures. *Abbreviations: 10-meter walk test (10MWT), 400-metre walk test (400mWT), 4-meter walk test (4mWT), 6-minute walk distance (6MWD), 6-minute walking test (6MWT), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), Duchenne muscular dystrophy (DMD), U.S. Food and Drug Administration (FDA), facioscapulohumeral dystrophy (FSHD), intraclass correlation coefficient (ICC), limb-girdle muscular dystrophy type R2 (LGMDR2), Letter of Intent (LOI), mean absolute error (MAE), minimal clinically important difference (MCID), manual muscle testing (MMT), Movement Disorder Society–Unified Parkinson’s Disease Rating Scale part III (MDS-UPDRS III), Mobilise-D consortium (MOBILISE-D), multiple sclerosis (MS), North Star Ambulatory Assessment (NSAA), Parkinson’s disease (PD), proximal femoral fracture (PFF), real-world walking speed (RWS), standard error of measurement (SEM), spinal muscular atrophy (SMA), stride length 50th centile (SL50C), stride length 95th centile (SL95C), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C), walking bout (WB).*

Data by Disease

Muscular Dystrophies

In 2023, the EMA qualified the first digital outcome for the use as primary endpoint in clinical trials for DMD. This outcome, the SV95C, represents the 5% fastest strides in daily living, measured with an inertial wearable device called Actimyo®. This achievement relies on its excellent metric properties (European Medicines Agency, n.d.-c). Accuracy was demonstrated in comparison with a motion capture (Mocap) gold standard in controls and by comparison with physiotherapist evaluation during a 6MWT in DMD patients. SV95C significantly correlated ($p < 0.001$) with the 6-minute walk distance (6MWD), North Star Ambulatory Assessment (NSAA) and the timed 4-stairs climb (4SC) at baseline and every 3 months during a 1-year follow-up. The intraclass correlation coefficient (ICC) calculated on 2 successive 1-month recording periods in 52 patients with DMD was 0.97 establishing an excellent reliability. SV95C could differentiate between patients and age-matched controls as well as DMD from different age groups. The sensitivity to detect negative change was demonstrated by statistically significant decline of the SV95C at each time point ($p < 0.001$) as early as 3 months ($n=81$).

These results have been replicated on independent populations of patients (European Medicines Agency, n.d.-c) and compared to large normative database (Poleur et al., 2021)

SV95C has already been used as secondary endpoint in phase 3 clinical trials (NCT05096221, NCT06138639, NCT04906460, NCT05524883, NCT03039686). Results from one of them has been published (NCT03039686) and confirms the good metric properties of SV95C. An ongoing multicentric longitudinal study (NCT05982119) is recruiting controls and patients living with DMD for longer than 2 years old as well as participants with other neuromuscular diseases including FSHD.

A longitudinal pilot study ($n=18$) using SV95C among others enrolled patients living with FSHD. This study showed its good reliability ($ICC > 0.9$), external validity as well as a significant decline over a 4 months-period.

Parkinson's Disease

We found no fully regulatory-qualified outcomes related to real-walking speed (RWS) in PD. However, we included two studies that is part of the MOBILISE-D initiative, and another conducted in collaboration with it. The latter, a 72-month study using AX3®, included 88 patients living with PD and 111 controls to assess real-world walking speed based on a 7-day recording period (Kirk et al., 2023). RWS was significantly different between PD and controls but did not correlate with MDS-UPDRS III score at walking bouts between 30 and 60 seconds. RWS more significantly declined in PD (-2 cm/s/year, $p = 0.014$) than in controls (-1 cm/s/year, $p = < 0.001$). A separate study from the same initiative used the same outcome measure but a different device in patients with various conditions (congestive heart failure, chronic obstructive pulmonary disease, MS, PD, proximal femoral fracture and controls). They showed on 15 patients living with PD that walking bout detection was accurate (0.92), but less sensitive (0.60) than laboratory conditions. The absolute error was 11cm/s and 17cm/s in laboratory and daily living conditions, respectively. A recent study shows that gait and walking activity measures reached acceptable reliability using the

same threshold of >12 hours of wear-time for at least 3 days (Buekers et al., 2025). The ongoing MOBILISE-D extension study (NCT05874739) is an observational study aimed to investigate the validity of digital mobility outcomes quantified from a device-agnostic analytical pipeline on a larger cohort (up to 411 participants with PD and 240 age and gender-matched controls).

Sarcopenia

We identified an accepted LOI from 2019 on the FDA website for the use of a waist worn triaxial accelerometer (actibelt®) to assess real-world walking speed. We identified one study that may serve as preliminary work for this LOI, as it utilises the same device to record various gait parameters. The study enrolled 217 patients with sarcopenia and 26 controls in a 25-weeks study. Patient wore a triaxial accelerometer on the waist for a minimum period of 5 days before each planned clinical site visit. Data were collected in 192 patients on 32 sites. The residual standard error for gait speed ranges from 7 to 9 cm/sec. The study found a weak to moderate relationship between short (4-minute) and long (6-minute and 400-meter) walking tests and daily living mean gait speed during short and long walking bouts, respectively (Mueller et al., 2019). This study is based on a validation study evaluating the accuracy of the actibelt® speed algorithm, “step wave”, which concluded that the deviation was less than 1% in step detection and less than 0.05 m/s in gait speed measurements compared to the reference, even for slow-walking subjects (Keppler et al., 2019).

Multiple Sclerosis

To date, no outcome measures related to real-world walking speed in MS have achieved regulatory qualification. We identified another accepted LOI on the FDA website for the use of a waist worn triaxial accelerometer (actibelt®) to assess real-world walking speed. A 2012 study (Motl et al., 2012) showed that in 51 patients living with MS, the actibelt® speed algorithm “SVM” overestimated the mean walking speed during a 6MWT compared to standard method. The absolute error ranged from 2 to 26 cm/s, with a strong linear association between the error and Expanded Disability Status Scale (EDSS) ($r = 0.68$, $p = 0.0001$) along with the average of actual and actibelt® walking speed ($r = 0.71$, $p = 0.0001$) in the overall sample. In association with the LOI, we identified an unpublished multicentre study involving 74 patients living with MS, which demonstrated that a 0.1 m/s decrease in mean daily living walking speed – measured with actibelt® over 7 consecutive days – approximately corresponded to a 2-point increase on the EDSS (Food and Drug Administration, n.d.-d). Evidence from the MOBILISE-D project indicates that reliable real-world digital mobility outcomes can be achieved in MS with more than 12 hours of daily wear over at least 3 days, independent of weekend inclusion and consistent across levels of physical capacity (Buekers et al., 2025).

Huntington Disease

Our review did not identify any outcome measures that are fully qualified by regulatory authorities in HD. MC10, the company that developed Biostamp®, a body-worn wearable sensor, submitted a LOI to the FDA in 2020. They aim to develop an outcome measure focused on the specific gait abnormality in HD for early detection and assessment of the disease progression in clinical trials. This LOI was rejected by regulatory authorities because their aim was to measure gait parameters that lacked a clear functional impact. We did not find any other submission or publication in relation with this initiative.

Quality Assessment

Given the challenges in identifying a single assessment tool suitable for all papers included in this review, we adopted a mixed approach. The MMAT was used for research papers evaluating digital outcome measures, while the JBI critical appraisal tools were applied to narrative papers. The quality of the narrative papers was excellent. All four papers satisfied all six criteria, indicating strong methodological rigor. For research papers, the overall quality was generally good; however, the most common weaknesses related to lack of clarity regarding population representativeness and missing outcome data.

IV. DISCUSSION

Digital health is currently a major focus area, as attested by the increasing availability and use of wearable devices, the number of publications and the existence of dedicated journals. Digital outcomes from wearable devices are believed to have the potential to accelerate drug development, even if the formal demonstration has not been achieved yet. Regulatory authorities have expressed growing interest (Haberkamp et al., 2019) in considering digital endpoints for drug approval. Beyond drug approval, wearable technology could also provide digital measures to assess disease progression in clinical practice and guide treatment strategy at the individual level (Pahwa et al., 2018). Devices are increasingly available, research on the topic is extensive, and dedicated journals exist. However, adoption remains limited. Understanding the reasons for this gap is essential to determine how it should be addressed.

First, our systematic review revealed that most studies were small-scale academic investigations, which often lacked robust datasets and a clearly articulated intention to pursue regulatory qualification. Nevertheless, they converge to demonstrate the feasibility of using wearable devices to assess medical conditions and the good compliance of patients, including in the paediatric population (Wiedmann et al., 2020). However, even large initiatives such as MOBILISE-D, a €50 million project funded by industry and the EU IMI project (European Commission's platform for Community Research and Development Information Service, n.d.), faced major obstacles.

The MOBILISE-D project has not yet delivered a validated functional digital mobility assessment tool or outcome (Mikolaizak et al., 2022). Still, it generated valuable insights and fostered collaboration with technology companies, clinicians, patient groups, and pharmaceutical companies. This collaborative model is a key strength. The focus on

a wide range of medical conditions including PD, chronic obstructive pulmonary disease, MS and recovery from proximal femoral fracture, made challenging an impactful regulatory achievement in any of them. The structure of a major grant-funded project as a time-limited project further challenges the possibility to achieve regulatory qualification. Similarly, in MS and sarcopenia, early efforts including FDA Letters of Intent and algorithm validation studies have shown technical feasibility but failed to meet the stringent clinical and regulatory requirements for qualification. In HD, a 2020 LOI submission by MC10 was ultimately rejected, highlighting the difficulty of aligning device output with disease-specific regulatory standards. In contrast, the qualification of the SV95C for DMD by the EMA demonstrates that long-term, focused efforts, including multiple studies with strong metric properties and patient-level data, can result in regulatory success. However, this outcome remains confined to a narrow scope of application and cannot be directly extrapolated to other conditions without further validation.

Qualification is time- and resource-consuming. Optimising project and study designs is essential. First, research efforts must align with regulatory expectations. This requires early and ongoing dialogue with agencies like the EMA and FDA. Second, long-term collaborations, between developers, clinicians, patient, and regulators is vital to ensure progress beyond the limits of individual projects or funding cycles. Third, studies should go beyond feasibility and compliance. They must rigorously evaluate the full psychometric properties of the outcome in target populations.

Another key strategy is to simplify the qualification process. Real-world gait assessment is relevant across a wide range of conditions, including arthrosis, obesity, and post-surgical recovery. Current regulatory frameworks require validation within a specific context of use. As a result, separate and extensive validation is needed for each medical condition. In contrast, the EMA provides a unified pathway for the approval of pain treatments across diseases (European Medicines Agency, n.d.-e) A similar regulatory approach could accelerate the use of digital outcomes. Bridging different context of use could support a faster implementation of digital outcomes across several indications. To promote generalisability, harmonised methodologies and transparent algorithms are also needed.

Beyond these primary steps, further challenges must be anticipated. Traditionally, regulatory evaluation of outcomes has been grounded in clinical meaning and patient relevance. For example, step count per day – measured via smartphone or other commercial devices – is clinically meaningful (Block et al., 2017; Watanabe et al., 2024) and easy to understand. However, daily variability limits its utility in clinical trials. Conversely, machine-learning-derived outcomes offer promises for prediction, early diagnosis, treatment selection, and personalised medicine. Yet this metrics may lack transparency and perceived clinical relevance among patients and physicians. Moreover, it is crucial to focus on patient-centred digital health technologies to empower patients to manage and follow their activity. These should include intuitive apps and interfaces that present clear, relevant information. Easy interpretation by patients and clinicians will improve engagement, compliance, and overall clinical utility.

Together, these efforts could streamline qualification and promote the integration of digital endpoints in both regulatory processes and clinical practice. Recently, frameworks have been published to harmonise the

development of patient-centred digital outcomes. All emphasise regulatory approval as a critical step toward integrating digital technologies into care (Espay et al., 2019a; Goldsack et al., 2020).

This systematic review has several limitations. First, the number of studies included in the systematic part of this review is small. This reflects the high specificity of our inclusion criteria and the limited volume of primary literature. To mitigate this, we complemented our systematic analysis with a narrative review. Second, we only reviewed the EMA and FDA websites, excluding other agencies such as PMDA in Japan or TGE in Australia. Lastly, we focused specifically on real-world walking speed, given its relevance across many conditions. A broader review of digital gait and mobility remains a future objective.

V. KEY INSIGHTS

Walking speed measured by wearable devices shows considerable promise in providing insightful data across a broad range of diseases and accelerate drug development. However, most published studies remain insufficient to obtain regulatory approval, which is a critical step towards expanding digital outcome's reach in clinical practice. Accordingly, further research is necessary to comprehensively evaluate the clinical relevance of digital outcomes and achieve validation across a broader range of pathologies beyond DMD. Validation pathways must also be simplified and frameworks harmonised. It is of the utmost importance that studies are designed so that they can support the regulatory qualification of digital outcomes. With this approach, not only will they increase knowledge in the community, but they will also increase the number of tools that can directly find routine use.

The reviews presented in the last two chapters reached a common conclusion: despite the strong interest in digital health within the scientific community, most studies remain small-scale academic initiatives, and only a few outcomes have achieved regulatory approval, with the majority still insufficiently validated.

PRELIMINARY WORK OF OUR RESEARCH GROUP

I. DUCHENNE MUSCULAR DYSTROPHY

DMD is a severe, rapidly progressive X-linked recessive neuromuscular disorder characterised by muscle weakening. It has an estimated incidence of 1 in 5000 males (Ryder et al., 2017). DMD is caused by out-of-frame mutations in the dystrophin gene, which leads to an absence or deficiency of the protein dystrophin and the degeneration of muscle fibres (Mah et al., 2016). The absence of dystrophin protein leads to progressive muscle necrosis, loss of independent ambulation by early adolescence, cardiomyopathy, respiratory insufficiency, and premature death in affected individuals (Mah et al., 2016).

Current therapeutic strategies to treat DMD focus either on restoring dystrophin (or surrogate proteins) at the sarcolemma to reinforce muscle fibres integrity (D'Ambrosio & Mendell, 2023), or on addressing secondary consequences of dystrophin deficiency and the progressive dystrophic pathology (Mercuri et al., 2024). Dystrophin restoration is being pursued with splice-switching antisense oligonucleotides (AONs), which convert out-of-frame deletions into shorter in-frame transcripts resulting in milder Becker muscular dystrophy (BMD) phenotype. Gene replacement using adeno-associated virus (AAV) vectors carrying micro-dystrophins is another promising approach. Efforts are also directed towards pharmacological upregulation of dystrophin-like proteins, such as utrophin (Fortunato et al., 2021).

These strategies are promising, and several clinical trials are ongoing or have already been carried out on DMD patients. The 6MWT has been used as the primary outcome measure in most published pivotal phase 3 trials in ambulant patients with DMD. Other used outcome measures include the 4-stair climb (4SC) and functional scales such as the NSAA in which participants are rated on their ability to perform standardised motor function tasks (Bushby et al., 2014; Charleston et al., 2017; Goemans et al., 2018; McDonald et al., 2017; Voit et al., 2014).

II. MONITORING OF MOVEMENT IN DUCHENNE MUSCULAR DYSTROPHY

In DMD, the standardised response mean (SRM) of traditional clinical outcome measures, which reflects their ability to detect change over time (Middel & van Sonderen, 2002), has historically been low. Consequently, pivotal trials required very large cohorts (over 100 patients per arm) and long durations of 18 to 24 months (e.g., NCT02851797, NCT02500381), which is challenging given the rarity of DMD and the urgency of developing effective treatments. To accelerate clinical development and investigate in parallel several approaches without being limited by the number of patients available, it became essential to validate more powerful outcome measures.

Since 2010, an academic team led by Prof. Laurent Servais has collaborated closely with the engineering company Sysnav (Vernon, France) to develop a CE-marked class I wearable medical device (wDHT) that passively and precisely records both upper and lower limb movements in daily life (Le Moing et al., 2016; Lilien et al., 2019). Unlike conventional clinic-based assessments, this digital technology captures continuous, ecologically valid data in real-world settings. From a single recorded movement, multiple outcomes can be derived. In ambulant patients, the identification and quantification of every individual stride make the calculation of stride length and stride speed possible. Subsequently, the distributions of stride length and speed can be computed, from which centile-based metrics can be extracted.

A major regulatory milestone was achieved when the EMA qualified the digital endpoint SV95C, initially as a valid secondary outcome (European Medicines Agency, n.d.-f) and later as a primary endpoint (European Medicines Agency, n.d.-c), in ambulant DMD trials. It thus became the first digital measure formally accepted by regulatory authorities for the use in clinical trials. SV95C represents the top 5% of the fastest strides spontaneously performed in daily life.

Importantly, the underlying wDHT technology increases statistical power not only in DMD but also in other neuromuscular disorders such as SMA (Annoussamy et al., 2021) and FSHD (Gidaro et al., 2022). These conditions share progressive muscle weakness but lack of other neurological features such as spasticity, ataxia, or complex movement disorders. Expanding digital mobility outcomes to broader neurological diseases remains a challenge, requiring disease-specific validation and the identification of disease-specific clinically meaningful digital outcome measures.

III. KEY INSIGHTS

Our research team participated to the qualification by the EMA of the SV95C for use as a primary endpoint in clinical trials for DMD. This work represents a first step towards generalising the use of wDHT across neuromuscular and neurodegenerative diseases, with the ultimate goal of transforming the way functional outcomes are captured in clinical research and care.

2

PART 2

RESEARCH OVERVIEW

GENERAL CONSIDERATIONS

I. SCOPE AND STAGE OF DEVELOPMENT OF THE RESULTS

This work relies on multiple studies conducted across different diseases. The findings from these studies are presented at varying stages of maturity. Such heterogeneity reflects differences in degree of validation, analytical verification, and the availability of longitudinal data. These disparities can partly be attributed to the initiation dates of these studies as well as to differences in access to funding, which in some cases accelerated the study progress. The varying levels of maturity may also be explained by the extent to which it was possible to rely on existing work in DMD for data analysis. In MS, for example, we were able to rely on previously established methodologies for gait assessment, whereas for other conditions, including PD and ALS, our collaborating engineering teams had to develop novel algorithms to identify new, disease-specific variables. Accordingly, while certain data included in this work have already been published, others are currently undergoing peer review, and some remain preliminary in nature. In the following chapters, we will discuss our work in detail on control populations, MS, ALS, and PD. Furthermore, some analyses, such as those related to the detection and quantification of upper limb movements, are still too immature to be included in this manuscript and should rather be the focus of future research.

II. METHODOLOGICAL CONSIDERATIONS

Studies included in this manuscript rely on a core methodology and shared objectives. Their aim is to identify and validate digital outcome measures collected with a wearable magneto-inertial device. The specific outcomes and algorithms used vary between studies, to capture the meaningful features of each disease. The following section outlines the methodology common to all studies. Study-specific details are discussed separately.

Device and Wear Protocol Choice

Basis for the Choice

Differences in IMUs can largely be attributed to the performance and quality of their two major components. The first is the software which includes sensor fusion algorithms (determining how gyroscope, accelerometer, and magnetometer data are combined and how drift and environmental disturbances are handled) as well as algorithm for signal processing and event detection approach. The second is the hardware, including gyroscopes, accelerometers and magnetometer. Differences in these components result in substantial variability in accuracy.

Even if the performance of some IMU has been evaluated for their applications in human movement analysis (Hori et al., 2020; Washabaugh et al., 2017), the wide variety of IMUs, the difference in collected outcomes and evaluation protocols make direct comparison challenging. Most published studies focused either on comparing software using the same hardware (Pacini Panebianco et al., 2018) or on comparing the same IMU placed at different locations. In contrast, few studies (L. Zhou et al., 2020) directly compared complete IMU systems under the same conditions. In the absence of these systematic head-to-head comparisons, we rely on previous validation of devices in other contexts of use to choose the one that seems to be most appropriate for our purpose.

In addition, as discussed in the section on magneto-inertial technology, a critical step prior to each study was the careful formulation of the research question: “what do we want to assess, and in which disease context?” Clearly defining this question is essential, as it directly informs the choice of wearing protocol, including the position of the sensors on the body, the duration of monitoring, and the frequency of data collection periods. For gait assessments, the preferred localisation of sensors seems to be the shank or foot based on previous literature (Pacini Panebianco et al., 2018; Prasanth et al., 2021). This research question-driven approach ensures that both the device and protocol fit study objectives.

ActiMyo®/ Syde® device

The wearable sensor data were collected using the ActiMyo® device (Sysnav, Vernon, France), as depicted in Figure 5. Patients were asked to wear two sensors on each ankle or on the ankle and wrist depending on the study protocol. These different configurations have a direct influence on what was recorded (upper limb versus more precise lower limb evaluation). Each sensor contains high precision triaxial accelerometers, triaxial gyroscopes, a temperature sensor, and a barometer (recording data at 100 Hz), that captured linear acceleration, angular velocity (in all directions), and barometric altitude.

The sensors were individually factory-calibrated to ensure the validity of each sensor’s measurements across a range of temperature, pressure, and dynamic environments. Syde® is the next generation of the ActiMyo® device. It uses the same sensor, but the design has been refined to better meet the patients’ aesthetic expectations.



Figure 5. Images of the ActiMyo® (A) and Syde® (B) devices.

Data Collection

In most studies presented in this manuscript, participants were instructed to wear the sensors during daytime. They were advised to remove the sensors for water-related activities such as showering or swimming.

Raw data were continuously collected throughout the day, stored in an internal memory and transferred to an internal USB drive in the docking station overnight when the patient removed and charged the device. From the docking station, encrypted and anonymised data were transferred securely, to a dedicated secure web cloud or remained on the USB drive (capacity to store up to 3 months of data).

Data Analysis

Gait Analysis

In our studies, a dedicated algorithm precisely and accurately reconstructed the trajectory of the ankle from raw data. The identification of each individual stride allowed a high-fidelity 3D trajectory reconstruction of each stride as well as continuous walking episodes detection. A walking episode was defined as a period of continuous walking without any interruption exceeding 15 seconds.

From the identification of every stride and walking episode during a daily-living recording period, we derived multiple variables. Candidate variables were selected based on established pathophysiological and clinical understanding specific to each disease.

Other Movement Detection

As these analyses are disease-specific, they will be discussed separately in each section.

CHAPTER 2

NORMATIVE DATA

This chapter presents the results published in the article entitled “Normative data on spontaneous stride velocity, stride length, and walking activity in a non-controlled environment” by M. Poleur et al., published in Orphanet Journal of Rare Diseases. This article is not reproduced in its entirety.

I. AIM

To properly interpret the longitudinal evolution of the SV95C over time in patient populations, it is necessary to understand the longitudinal evolution in subjects without muscle conditions within the same age range, in particular between 5 and 18 years old, which is the age range mostly targeted in clinical trials of ambulant DMD patients and during which growth or maturational factors may significantly interfere with measures (Goemans et al., 2013; Hogrel et al., 2020). Therefore, we conducted a longitudinal study in ambulant healthy subjects between 5 and 85 years of age to evaluate the changes in SV95C over 12 months.

II. METHOD

Study Design

ActiLiège is a monocentric academic study that was conducted in the Reference Centre for Neuromuscular Disease in Liège, Belgium between July 2017 and September 2019 with grant funding from Action Duchenne. The protocol was approved by the local ethics committee in Liège (N/Ref:1646). Before inclusion, all participants or parents or legal guardians provided written informed consent for participation and publication.

Participants

The initial protocol planned to include a maximum of 130 healthy subjects to gather a distribution of about 5–10 patients per age year in children and a group of 30 adults. Given difficulties in recruiting mainly adult controls, 91 healthy subjects above the age of 5 years were finally assessed at baseline and 84 were assessed after 12 months. The exclusion criteria were occurrence of surgery or recent trauma (less than six months) in the upper or lower limbs; participating in sport at a high (national) level; pregnant or breastfeeding women; occurrence of muscular, neurological, infectious, acute, or chronic inflammatory disease within three weeks of inclusion date; and occurrence of orthopaedic, neuromuscular, or neurological disease with an impact on the quality of walk.

Demographic data as well as medical and surgical histories were obtained during the baseline visit. A full physical examination, including weight, height, and vital signs, was performed at the first visit and at the 12-month visit. The subjects performed the 6MWT while wearing the sensors at baseline and at 12 months. They also performed

the 4SC, rise from floor (RFF), and 10-metre walk test (10MWT). All tests were conducted by trained and certified physiotherapists from the neuromuscular centre.

Timed Tests

The subjects performed the 6MWT according to the modified American Thoracic Society (ATS) guidelines (McDonald et al., 2010). For RFF, trained examiners recorded the time taken by the patient to complete the task of rising from supine to standing as fast as possible, using a stopwatch. The test was performed three times with a 1-minute rest between each trial. We kept the best performance. For the 4SC, the subject had to climb a 4-step flight of stairs as fast as possible. The test was performed three times with a 1-minute rest between each trial. We kept the best performance. For the 10MWT, the subject had to walk or run for 10 metres in a straight line. We recorded the time taken to complete the task as fast as possible. The test was performed three times with a 1-minute rest between each trial. We kept the best performance.

Movement Monitoring

According to the EMA, for the purposes of qualification, a recording is considered as valid if it includes at least 50 hours of recording; optimally it should include 180 hours of recording (European Medicines Agency, n.d.-c). We studied three different variables: stride length, stride velocity, and the number of meters walked per hour. Stride length and stride velocity were studied as the medians (SL50C and SV50C) or the 95th centiles (SL95C or SV95C).

Statistical Analysis

Analysis was first performed on the whole sample and then we analysed children (5 to 17 years) and adults (18 years and older) separately. Then within these groups, we analysed male and female subgroups. We used a series of Wilcoxon rank-sum test to compare subgroups. We then performed correlation analyses using Spearman's rank correlation coefficient based on accelerometer measures, time test performances, age, and height. Finally, we use the Wilcoxon test to assess the evolution of each measure over 12 months. For compliance analysis, we used the 50-h and 180-h thresholds as these two thresholds were defined in the EMA qualification document as acceptable and optimal, respectively (European Medicines Agency, n.d.-c). All analyses were performed using IBM's SPSS Statistics software. The limit of statistical significance was set to 0.05.

III. RESULTS

Population

We included 91 healthy individuals (41 males (45.1%) and 50 females (54.9%)), with a mean age of 16 years 2 months (SD = 15.4 years; range: 6–85 years). Seven participants withdrew between the baseline, and the follow-up visit for personal reasons. A flow chart of subject participation is shown in Figure 6. The demographic and clinical characteristics of participants whose baseline data were analysed, as well as ActiMyo® variables, are provided in Table 6.

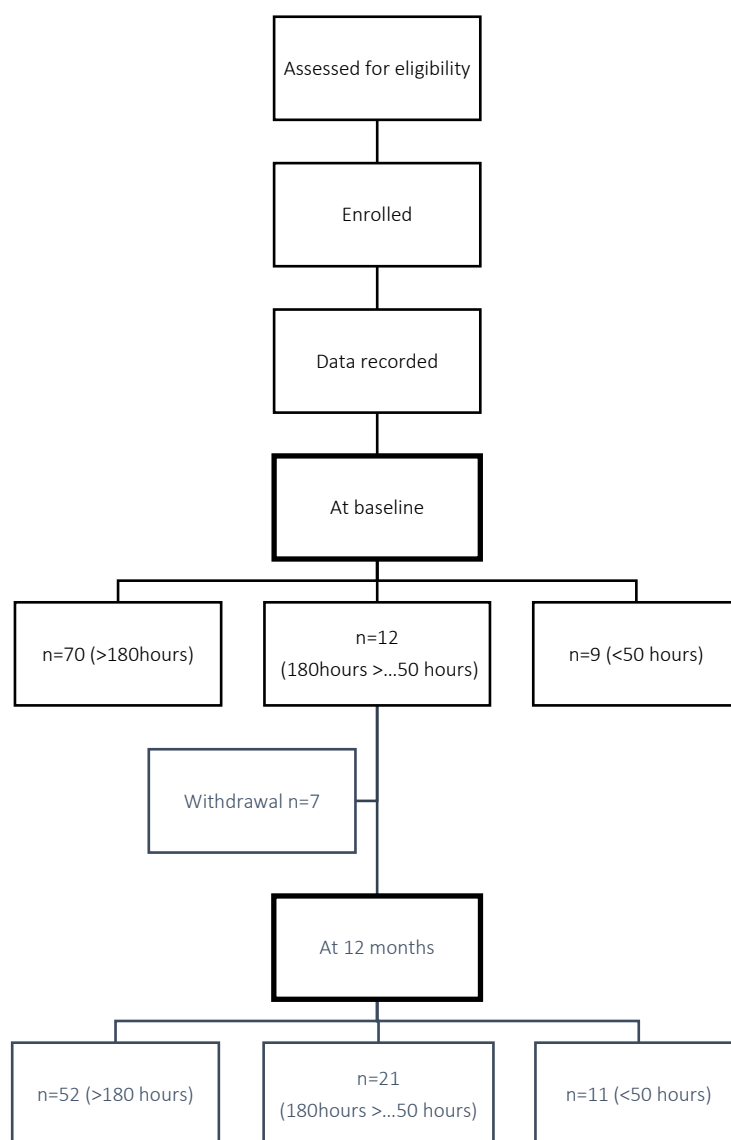


Figure 6. Flow chart displaying the compliance and inclusion of subjects. *Withdrawals resulted from loss of follow up (5 subjects) and withdrawal by the subject (2 subjects).*

Characteristics			
	Children	Adult	All
Sample size	65	17	82
Age (years): mean $\pm$ SD	10.1 $\pm$ 2.8	43.0 $\pm$ 18.9	16.9 $\pm$ 16.0
[range]	[6.0 – 17.6]	[18.0– 84.3]	[6.0 – 84.3]
Sex: number of female (%)	34 (52.3%)	12 (70,6%)	46 (56.0%)
Height (centimetres): mean $\pm$ SD [range]	137.8 $\pm$ 14.6 [114.0 – 173.3]	167.5 $\pm$ 10.6 [153.2 – 195.0]	144.0 $\pm$ 18.3 [114.0 – 195.0]
6MWT (meters): mean $\pm$ SD [range]	606.0 $\pm$ 64.1 [464.0 – 761.0]	551.5 $\pm$ 82.0 [436.0 – 716.0]	594.7 $\pm$ 71.2 [436.0 – 761.0]
4SC (s): mean $\pm$ SD [range]	1.3 $\pm$ 0.3 [0.9 – 2.3]	1.6 $\pm$ 0.4 [1.1 – 2.3]	1.4 $\pm$ 0.3 [0.9 – 2.3]
RFF (s): mean $\pm$ SD [range]	1.6 $\pm$ 0.2 [1.0 – 2.2]	2.7 $\pm$ 0.9 [1.2 – 4.9]	1.8 $\pm$ 0.6 [1.0 – 4.9]
10MWT (m): mean $\pm$ SD [range]	4.7 $\pm$ 0.7 [3.1 – 7.2]	5.1 $\pm$ 0.8 [4.1– 7.3]	4.8 $\pm$ 0.8 [3.1 – 7.3]
Distance/hour (m/h): mean $\pm$ SD [range]	270.2 $\pm$ 86.5 [39.9 – 484.4]	246.4 $\pm$ 89.5 [119.6 – 433.0]	265.2 $\pm$ 87.2 [39.9 – 484.4]
SV50C (m/s): mean $\pm$ SD [range]]	1.0 $\pm$ 0.1 [0.9 – 1.3]	1.1 $\pm$ 0.1 [0.7 – 1.3]	1.0 $\pm$ 0.1 [0.7 – 1.3]
SV95C (m/s): mean $\pm$ SD [range]	2.6 $\pm$ 0.4 [1.6 – 3.6]	1.6 $\pm$ 0.3 [1.1 – 2.3]	1.1 $\pm$ 0.3 [1.1 – 3.6]
SL50C (m): mean $\pm$ SD [range]	1.0 $\pm$ 0.1 [0.8 – 1.4]	1.2 $\pm$ 0.1 [0.8 – 1.5]	1.1 $\pm$ 0.1 [0.8 – 1.5]
SL95C (m): mean $\pm$ SD [range]	1.7 $\pm$ 0.2 [1.4 – 2.3]	1.5 $\pm$ 0.2 [1.1 – 1.8]	1.7 $\pm$ 0.2 [1.1 – 2.3]

Table 6. Demographic and clinical characteristics of participants who recorded more than 50 hours. *Data are expressed in mean $\pm$ standard deviation (SD) [Min–Max]. Abbreviations: 4-Stair Climb (4SC), 6-minute walking test (6MWT), 10-metre walk test (10MWT), Rise from floor (RFF), stride length 50th centile (SL50C), stride length 95th centile (SL95C), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C).*

Statistical analysis was performed on data from the 82 participants who achieved more than 50 hours of recording at baseline. For further analysis, healthy subjects were distributed into two age subgroups: those 5 to 17 years of age and those older than 18 years. The first subgroup was composed of 65 participants, 34 of whom were females (52.3%). The second group was composed of 17 participants, of whom 12 were females (70.6%).

The two age groups differed from each other in most measures including height, 6MWD, 4SC, RFF, and stride characteristics (SV50C, SV95C, SL50C and SL95C). Younger subjects were shorter ($p<0.001$) but had a higher 6MWD ($p=0.011$) than adults. The younger group also performed better at 4SC ($p=0.001$) and RFF ($p<0.001$). The groups did not differ significantly in 10MWT performance ($p=0.079$). Regarding magneto-inertial measures, the groups did not differ significantly in the distance walked per hour ($p=0.215$). SV50C tended to be higher in the adult group ($p=0.047$), whereas SV95C was higher in children ($p=0.001$). We found a similar pattern in stride length measures: SL50C was higher in adults ($p=0.001$) but SL95C was higher in children ($p=0.001$). The ratio between the SV95 and the SV50c was three times higher in younger subjects than in adults, and the ratio between SL95C and SL50C was twice higher in younger subjects, which seems to indicate a more stereotyped walking patterns in adults.

Compliance in Wearing the Device

Among the 91 healthy controls who wore the wearable device for one month, 90% recorded more than 50 hours, and 77% recorded more than 180 hours at baseline. During the second period, 86% recorded more than 50 hours, and 73% recorded more than 180 hours. The main reason reported by subjects who recorded less than 50 hours was 'technical issues'. There was no age or gender effect evident on the recording duration (data not shown).

Correlations Between Timed Tests, Stride Parameters and Walking Activity.

Table 7 presents correlation coefficients between stride parameters obtained using the wearable device and clinical measures at baseline in both subgroups. We also present data from the 82 subjects who achieved more than 50 hours of recording at baseline. 6MWD was significantly correlated with SV50C, SV95C, and SL95C in the younger group. In the adult group, 6MWD was only correlated with 'top performance' measures SV95C and SL95C. In the younger population, the impact of age and height was more obvious than in the adult population (Table 7). Among the group aged 5 to 17 years, height was highly correlated with age, 6MWD, 10MWT, SV50C, SL50C, and weakly correlated with SV95C and SL95C. In adults, height was only correlated with stride length measures SL50C and SL95C. We found no correlation between recording duration and stride length, stride velocity, or walking activity (distance/h, $p=0.323$; SV50C, $p=0.466$; SV95C, $p=0.664$; SL50C, $p=0.723$ and SL95C, $p=0.798$).

	Age	Height	6MWT	4SC	RRF	10MWT	Distance	SVC50	SVC95	SLC50	SLC95C	
Age		0.909** <i>p</i> =0.000	0.6** <i>p</i> =0.000	-0.142 <i>p</i> =0.261	-0.011 <i>p</i> =0.932	-0.479** <i>p</i> =0.000	0.03 <i>p</i> =0.816	0.621** <i>p</i> =0.000	-0.231 <i>p</i> =0.064	0.869** <i>p</i> =0.000	0.312* <i>p</i> =0.011	5–17 y.
		-0.134 <i>p</i> =0.609	-0.703** <i>p</i> =0.002	0.14 <i>p</i> =0.592	0.447 <i>p</i> =0.083	0.434 <i>p</i> =0.082	0.115 <i>p</i> =0.660	-0.206 <i>p</i> =0.428	-0.738* <i>p</i> =0.001	-0.091 <i>p</i> =0.729	-0.561* <i>p</i> =0.019	≥18 y.
Height	0.927** <i>p</i> =0.000		0.538** <i>p</i> =0.000	-0.163 <i>p</i> =0.195	0.028 <i>p</i> =0.822	-0.407** <i>p</i> =0.001	-0.036 <i>p</i> =0.778	0.552** <i>p</i> =0.000	-0.269* <i>p</i> =0.030	0.876** <i>p</i> =0.000	0.274* <i>p</i> =0.027	5–17 y.
			0.061 <i>p</i> =0.815	-0.288 <i>p</i> =0.262	0.01 <i>p</i> =0.970	-0.326 <i>p</i> =0.201	0.108 <i>p</i> =0.680	0.116 <i>p</i> =0.656	0.254 <i>p</i> =0.326	0.678** <i>p</i> =0.003	0.668** <i>p</i> =0.003	≥18 y.
6MWT	0.122 <i>p</i> =0.275	0.157 <i>p</i> =0.159		-0.033 <i>p</i> =0.797	-0.183 <i>p</i> =0.144	-0.595** <i>p</i> =0.000	0.11 <i>p</i> =0.383	0.454** <i>p</i> =0.000	0.034 <i>p</i> =0.789	0.518** <i>p</i> =0.000	0.374** <i>p</i> =0.002	5–17y.
				0.054 <i>p</i> =0.837	-0.409 <i>p</i> =0.116	-0.373 <i>p</i> =0.141	-0.078 <i>p</i> =0.765	0.444 <i>p</i> =0.074	0.858** <i>p</i> =0.000	0.103 <i>p</i> =0.694	0.485* <i>p</i> =0.048	≥18 y.

4SC	0.184	0.137	-0.135		0.515**	0.155	-0.232	-0.219	-0.117	-0.163	-0.144	5–17y.
	<i>p</i> =0.097	<i>p</i> =0.22	<i>p</i> =0.226		<i>p</i> =0.000	<i>p</i> =0.218	<i>p</i> =0.062	<i>p</i> =0.080	<i>p</i> =0.354	<i>p</i> =0.195	<i>p</i> =0.252	
					0.63**	0.415	-0.43	-0.087	0.05	-0.27	-0.187	≥18 y.
					<i>p</i> =0.009	<i>p</i> =0.097	<i>p</i> =0.085	<i>p</i> =0.739	<i>p</i> =0.848	<i>p</i> =0.294	<i>p</i> =0.473	
RFF	0.418**	0.389**	-0.334**	0.607**		0.089	-0.263*	-0.222	-0.418**	-0.1	-0.405**	5–17y.
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.002	<i>p</i> =0.000		<i>p</i> =0.482	<i>p</i> =0.034	<i>p</i> =0.076	<i>p</i> =0.001	<i>p</i> =0.428	<i>p</i> =0.001	
						0.362	-0.241	-0.018	-0.385	0	-0.256	≥18 y.
						<i>p</i> =0.169	<i>p</i> =0.368	<i>p</i> =0.948	<i>p</i> =0.141	<i>p</i> =1.000	<i>p</i> =0.339	
10MWT	-0.143	-0.149	-0.565**	0.256*	0.181		-0.426**	-0.477**	-0.09	-0.493**	-0.298*	5–17y.
	<i>p</i> =0.199	<i>p</i> =0.183	<i>p</i> =0.000	<i>p</i> =0.020	<i>p</i> =0.106		<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.477	<i>p</i> =0.000	<i>p</i> =0.016	
							-0.201	-0.331	-0.306	-0.331	-0.319	≥18 y.
							<i>p</i> =0.439	<i>p</i> =0.195	<i>p</i> =0.232	<i>p</i> =0.195	<i>p</i> =0.213	

	Age	Height	6MWT	4SC	RRF	10MWT	Distance	SVC50	SVC95	SLC50	SLC95C	
Distance	-0.083*	-0.135	0.101	-0.285**	-0.298**	-0.362**		0.451**	0.437**	0.148	0.281*	5–17y.
	<i>p</i> =0.461	<i>p</i> =0.225	<i>p</i> =0.365	<i>p</i> =0.009	<i>p</i> =0.007	<i>p</i> =0.001		<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.241	<i>p</i> =0.023	
								0.691**	0.157	0.659**	0.252	≥18 y.
								<i>p</i> =0.002	<i>p</i> =0.548	<i>p</i> =0.004	<i>p</i> =0.328	
SVC50	0.513**	0.499**	0.336**	-0.077	-0.01	-0.377**	0.455**		0.114	0.786**	0.418**	5–17y.
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.002	<i>p</i> =0.493	<i>p</i> =0.929	<i>p</i> =0.000	<i>p</i> =0.000		<i>p</i> =0.366	<i>p</i> =0.000	<i>p</i> =0.001	
									0.542*	0.684**	0.449	≥18 y.
									<i>p</i> =0.025	<i>p</i> =0.002	<i>p</i> =0.071	
SVC95	-0.609**	-0.598**	0.271*	-0.3**	-0.631**	-0.203	0.389**	-0.053		-0.098	0.728**	5–17y.
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.014	<i>p</i> =0.006	<i>p</i> =0.000	<i>p</i> =0.068	<i>p</i> =0.000	<i>p</i> =0.636		<i>p</i> =0.436	<i>p</i> =0.000	
										0.417	0.748**	≥18 y.
										<i>p</i> =0.096	<i>p</i> =0.001	

SLC50	0.829**	0.883**	0.212	0.057	0.289**	-0.276*	0.081	0.74**	-0.414**		0.455**	5–17y.
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.055	<i>p</i> =0.610	<i>p</i> =0.009	<i>p</i> =0.012	<i>p</i> =0.469	<i>p</i> =0.000	<i>p</i> =0.000		<i>p</i> =0.000	
											0.721**	≥18 y.
											<i>p</i> =0.001	
SLC95C	-0.099*	-0.037	0.465**	-0.224*	-0.494**	-0.328**	0.289**	0.293**	0.734**	0.16		5–17y.
	<i>p</i> =0.375	<i>p</i> =0.744	<i>p</i> =0.000	<i>p</i> =0.043	<i>p</i> =0.000	<i>p</i> =0.003	<i>p</i> =0.009	<i>p</i> =0.008	<i>p</i> =0.000	<i>p</i> =0.152		
												≥18 y.

Table 7. Correlation between accelerometer measures and clinical measures (Spearman’s correlation coefficient; $p<0.05^*$, $p<0.01$). *Lower part: correlation on the whole sample. Upper part: correlation on the two age groups. Abbreviations: 4-Stair Climb (4SC), 6-minute walking test (6MWT), 10-metre walk test (10MWT), rise from floor (RFF), stride length 50th centile (SL50C), stride length 95th centile (SL95C), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C).*

Gender Effect

In the adult population, males showed statistically significantly higher SL50C ($p=0.009$) and SL95C ($p=0.001$), probably because they are on average taller than women in the cohort ($p=0.048$). There was no other difference between males and females in the adult group. In contrast, in the younger population, male subjects were taller than female subjects, but we did not detect significant differences in any qualitative real-life walking parameter between the two subgroups.

Longitudinal Data

The aggregated changes over 12 months are presented in Table 8, and the individual trajectories are illustrated in Figure 7. We present data on the 73 patients who achieved more than 50 hours of recording both at baseline and on follow-up visits. Given the effects of growth, we investigated two subgroups separately. In the younger group, we observed a significant increase in functional measures (6MWD, 4SC, 10MWT) over 1-year. Of the variable instrumented measures, only SL50C increased over 1-year. We did not observe a significant change over 1-year in adults in stride length, stride velocity, distance walked, 6MWD, or RFF with the exception of a slight improvement in the 10MWT performance.

Subgroup	5–17years old		Over 18 years old	
Characteristics	Mean $\pm$ SD	p-value	Mean $\pm$ SD	p-value
Δ 6MWD (m)	33.6 $\pm$ 50.302	$p=0.000^{**}$	14.87 $\pm$ 46.649	$p=0.191$
Δ 4SC (s)	-0.11 $\pm$ 0.288	$p=0.004^{**}$	-0.02 $\pm$ 0.463	$p=0.875$
Δ RFF (s)	-0.07 $\pm$ 0.336	$p=0.293$	-0.24 $\pm$ 0.736	$p=0.239$
Δ 10MWT (s)	-0.76 $\pm$ 0.77	$p=0.000^{**}$	-0.52 $\pm$ 0.632	$p=0.011^{*}$
Δ Distance (m/h)	-17.23 $\pm$ 76.17	$p=0.059$	9.38 $\pm$ 67.15	$p=0.609$
Δ SV50C (m/s)	0.01 $\pm$ 0.078	$p=0.359$	0.01 $\pm$ 0.154	$p=0.691$
Δ SV95C (m/s)	-0.12 $\pm$ 0.447	$p=0.112$	0.12 $\pm$ 0.389	$p=0.955$
Δ SL50C (m)	0.05 $\pm$ 0.06	$p=0.000^{**}$	0.01 $\pm$ 0.095	$p=0.427$
Δ SL95C (m)	0,02 $\pm$ 0.184	$p=0.241$	0,04 $\pm$ 0.133	$p=0.691$

Table 8. Evolution of measures over 12 months. Time effect was assessed by a rank Wilcoxon test for single sample (null hypothesis: median=0). Significance level $p \leq 0.01^{**}$, $p \leq 0.05^{*}$. Abbreviations: 4-stair climb (4SC), 6-minute walk distance (6MWD), 10-metre walk test (10MWT), change from baseline (Δ), rise from floor (RFF), stride length 50th centile (SL50C), stride length 95th centile (SL95C), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C).

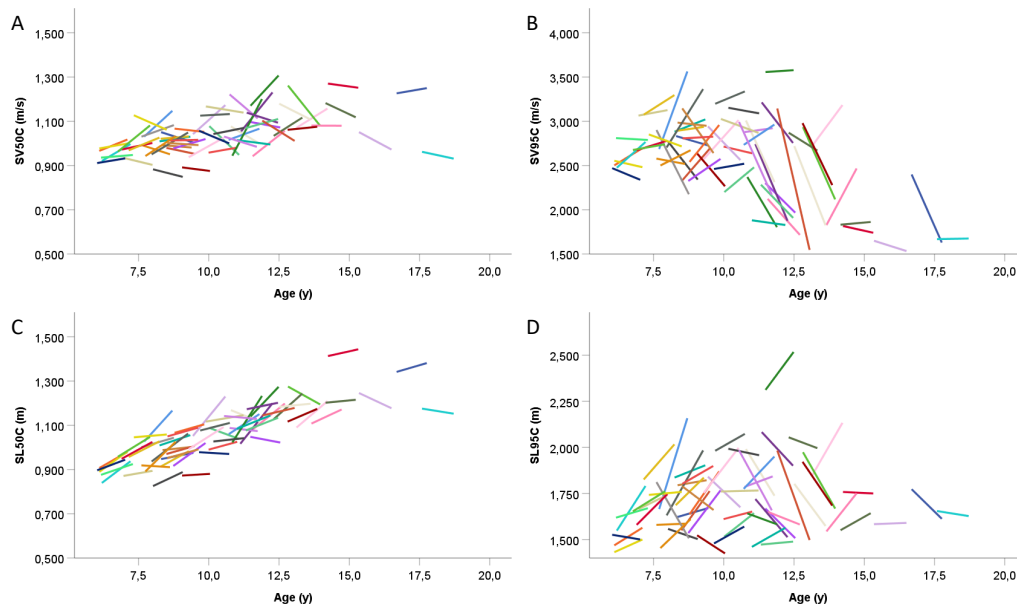


Figure 7. One year evolution of SV50C (A), SV95C (B), SL50C (C) and SL95C (D) in subjects aged 5 to 17 years. Abbreviations: stride length 50th centile (SL50C), stride length 95th centile (SL95C), stride velocity 50th centile (SV50C), stride velocity 95th centile (SV95C).

IV. DISCUSSION

Through this study, we provide normative data for spontaneous stride velocity, stride length and walking distance/hour obtained passively with a wearable device during a 1-month recording period in a non-controlled setting and the 1-year evolution thereafter. The overall compliance with device use was good. More than 90% of subjects wore the device more than the minimum requirement of 50 hours, which indicates that wearing devices at the ankle and at the wrist for 1 month was acceptable for most of participants. The main reason given for data collection below the 50-hour threshold was ‘technical issues’, and compliance was not influenced by gender or age. In addition, the recording duration did not influence the variables that were studied.

As expected, results of timed tests were growth dependent (Hoskens et al., 2019). We also observed the influence of height (in adults) and height and growth (in children) on stride length. These results support previous findings (Dusing & Thorpe, 2007; Pierrynowski & Galea, 2001). Height did not influence SV95C, for which only a very weak inverse correlation was found with height in the children only. In children, all correlations between age, height and stride length or speed were much weaker with top performance as measured by the 95th centile than with median values. Independence of growth is an advantage in clinical trials that are conducted in children over 1 or 2 years, especially in DMD where growth is altered by steroid use.

In comparison with ambulant DMD patients of the same age, healthy children present a 67.3% higher SV95C (European Medicines Agency, n.d.-c). The difference for other variables was not as extreme, and there is some overlap between DMD and control participants (SL50C 31.39%, SL95C 52.41%, SV50C 25.72%, distance

walked/hour 63.13%) (European Medicines Agency, n.d.-c). SV95C was stable over the 1-year period in controls but significantly and constantly decreased in subjects with DMD. In DMD patients, there is a significant correlation between SV95C and all timed tests (European Medicines Agency, n.d.-c). We did not find such correlations in controls, which is probably related to the fact that weakness constitutes a common limiting factor on 6MWD and SV95C in patients with DMD, strengthening the correlation in this group.

Gathering normative data is crucial in the validation process of an outcome measure, as it allows identification of potentially confounding variables such as age, height, or gender. For a specific outcome, the normative data can either show a strong ceiling effect, as is the case for most of normative scales such as CHOP Intend, NSAA, and Motor Function Measure (MFM) (Biogen, n.d.; De Lattre et al., 2013; Klingels et al., 2015; Kolb et al., 2016), or increases with age, as is the case for strength (Hogrel et al., 2020; Servais et al., 2013) and the 6MWD (Goemans et al., 2013).

The limitation of this study resides in the small number of controls per subgroup (age and gender), principally related to the limited availability of recording devices. Given the number of subjects, we did not study the seasonal influence on the parameters. It is likely that a seasonal analysis would need to take weather conditions into account, as they are more likely to influence walking behaviour than does the time of year, and would require continuous recording over 1-year, which could be burdensome in controls. During the study, participants wore devices on both wrist and ankle. The analysis of upper limb movement in control patients is complex, since there is an interference with movement produced during the ambulation. The results will therefore be presented elsewhere in comparison with the upper limb measures in ambulant and non-ambulant DMD patients.

V. KEY INSIGHTS

This study provides evidence that normative data regarding stride length and velocity in a home-based environment with wearable sensors is feasible. These normative data will allow us to express a patient's data as a percentage of predicted value for age or height and to identify those variables that have important confounding factors. Further work is required to enable analysis of ambulation and upper limb function in various diseases using medical device for real-life mobility measurement. Future research should focus on exploring new fields of neurological disease and the creation of algorithms to study upper limb function, falls, or ataxia.

CHAPTER 3

MULTIPLE SCLEROSIS

The following chapter presents the results published in the article entitled “Stride-level measurement of gait as an early sensitive marker of disability progression in ambulatory patients with multiple sclerosis” by M. Poleur et al., published in *eClinicalMedicine*. This article is not reproduced in its entirety.

I. CLINICAL OVERVIEW

MS is an acquired inflammatory demyelinating disorder of the central nervous system that affects 2.9 million individuals worldwide (Walton et al., 2020) with an increasing prevalence. It is characterised by inflammation and neurodegeneration, leading to a broad spectrum of clinical manifestations and levels of disability with gait impairment as one of the most prevalent MS symptoms (Attfield et al., 2022).

Patients with MS have traditionally been divided into three categories based on the clinical disease course (Lublin, 2014)(relapsing-remitting, secondary-progressive, and primary-progressive) in routine care, as well as in clinical development and during drug approval. High-efficacy therapies have been shown to effectively control relapse biology, whereas treatments targeting chronic MS progression have generally yielded limited results (Sriwastava et al., 2024), with a few exceptions (Fox et al., 2024). Ongoing advances in understanding MS pathophysiology have opened the way for treatments targeting chronic disability progression. MS drug development timelines remain long, without effective predictors or surrogates for clinical outcomes (Ontaneda et al., 2015). MS progression represents both the key therapeutic and measurement need in MS as the development of treatments requires quantifiable, objective, and reliable outcome measure reflecting disability progression (European Medicines Agency, n.d.-g). These outcome measures should accurately capture disability progression in an appropriate MS cohort within a reasonable clinical trial timeframe.

Progressive ambulation impairment is considered a major consequence of MS. It significantly impacts the quality of life of MS patients (Heesen et al., 2018), and as such, is captured by traditional gold standard clinical assessments such as the EDSS or Timed 25-Foot Walk (T25FW) (European Medicines Agency, n.d.-g). Most studies reporting the use of wDHT to assess ambulation in MS focused on physical activity or step count (Dalla Costa et al., 2024; Goldman et al., 2025) measured by commercially available mainstream devices or smartphone sensors (Woelfle et al., 2023). Some digital outcomes have shown encouraging metric properties (Dalla Costa et al., 2024; Goldman et al., 2025), reaching known-group and convergent validity but very few demonstrated sensitivity to detect change (Polhemus et al., 2021). Despite increasing regulatory interest in walking speed as an outcome in MS (Food and Drug Administration, n.d.-d) and strong evidence in the literature supporting its clinical relevance (Karatsidis et al., 2025), none of the currently available measures have yet been sufficiently validated to achieve regulatory approval. Beyond regulatory approval, robust evidence is needed to demonstrate the added value of

digital outcome measures. To date, wDHTs have not demonstrated sufficient predictive value or undergone rigorous validation to meaningfully support drug development decisions or even drug approval.

II. AIM

By analysing gait at the level of individual strides, our objective was to develop and validate digital mobility outcomes that are accurate, acceptable, reliable, and sensitive to the progressive impact of MS on ambulation. We specifically aimed to assess the analytical and clinical validity of stride-level mobility outcomes derived from daily-living ambulation.

III. METHODS

Study Design and Populations

The design and objectives of both studies are presented in Figure 8.

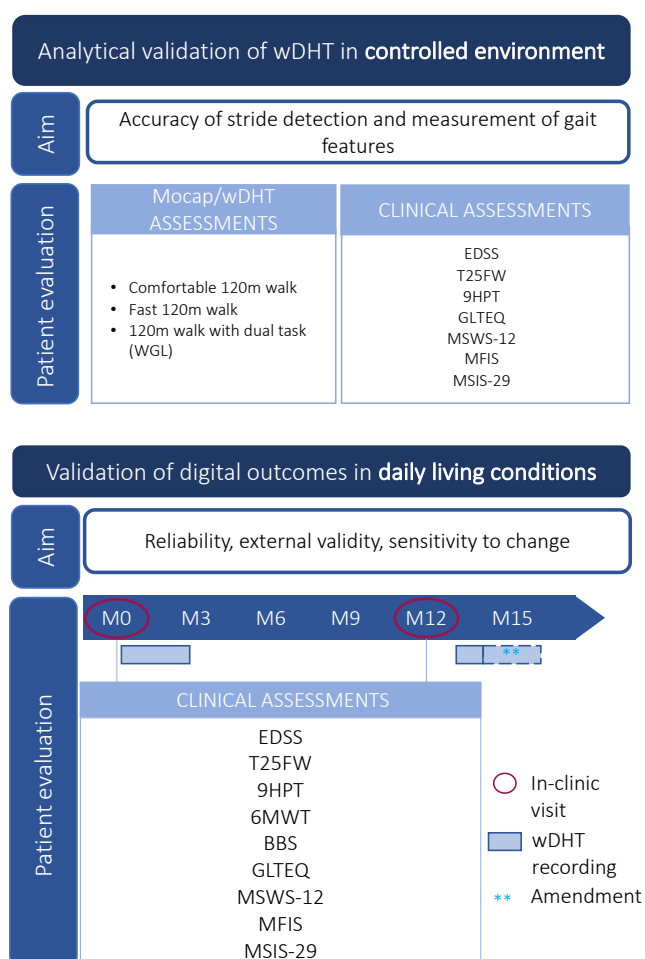


Figure 8. Project overview. Abbreviations: 6-minute walking test (6MWT), 9-Hole Peg Test (9HPT), Berg Balance Scale (BBS), Expanded Disability Status Scale (EDSS), Godin Leisure Time Exercise Questionnaire (GLTEQ), Modified Fatigue Impact Scale (MFIS), motion capture (Mocap), Multiple Sclerosis Impact Scale (MSIS-29), 12-item Multiple Sclerosis Walking Scale (MSWS-12), Timed 25-Foot Walk (T25FW), wearable digital health technology (wDHT), Word Generation List (WGL).

ActiMS Controlled Environment Study

We conducted a cross-sectional, single-centre study, called “ActiMS Controlled Environment”, from September 12, 2021, to September 18, 2021, to validate the performance of the wDHT in detecting strides and measuring the gait features in participants diagnosed with MS, at the Citadelle Hospital of Liège, Belgium. The inclusion criteria were a confirmed diagnosis according to the 2017 McDonald criteria, age between 18 and 65 years, an EDSS ≤ 5.5 , no clinical and/or radiological relapse within the previous 3 months, and stable disease-modifying therapy for at least 2 months before inclusion. The exclusion criteria were significant cognitive disorders based on the investigator’s clinical judgment, other past or current diseases that could impact the patient's motor function, and recent surgery or trauma.

ActiMS Study in Daily Living Conditions

We conducted a longitudinal, multicentre cohort study to develop a digital endpoint with robust clinical properties in people with MS at five sites in Belgium and France. Data were collected from March 2021 to January 2024. The long-term follow-up of this study is ongoing. Progression was defined according to the 2014 Lublin criteria (Lublin, 2014). Eligibility criteria were identical to those of the controlled environment study. Patients included in the controlled environment study were also eligible to participate in this study.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval of the controlled environment validation study (NCT04888689) was obtained from the Ethics Committees of the University Hospital of Liège and the Regional Hospital of Liège. All participants were fully informed of the study protocol and provided written informed consent.

Approval of the protocol of the longitudinal cohort study (NCT04882891) was obtained from Ethics Committees of all participating sites. After receiving information about the study, patients provided written informed consent.

Both studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Data Collection and Devices

Clinical Assessment

All clinical measures were performed at each visit in both studies except for the 6MWT and Berg Balance Scale (BBS), which were not performed in the Controlled Environment Study. The EDSS, T25FW and Nine-Hole Peg Test (9HPT) (22) were performed as gold standard clinical assessments of patients with MS. We incorporated the 6MWT (23) and the BBS to gather data on walking endurance and ataxia, respectively. The EDSS was performed by a physician (neurologist or neurology resident) trained in the protocol. Other clinical evaluations were conducted by physiotherapists or MS nurses trained in the protocol and its assessment procedures.

Patient-reported outcome (PRO)

Patient-reported outcome measures, such as the Godin Leisure Time Exercise Questionnaire (GLTEQ), 12-item Multiple Sclerosis Walking Scale (MSWS-12), Modified Fatigue Impact Scale (MFIS), and Multiple Sclerosis Impact Scale (MSIS-29), were collected at each visit in both studies.

Data Collection

Clinical data were collected on both paper and electronic case report forms with the latter hosted on Research Electronic Data Capture, a secure, web-based application designed for data collection

Gait Analysis in Controlled Environment

Patients were equipped with a wDHT (ActiMyo® device, Sysnav, Vernon, France) as well as motion-capture markers (OptiTrack®, NaturalPoint, Oregon, U.S.A.) on both ankles. Mocap markers were fixed to the wDHT. Participants completed three walking exercises: fast walking speed, comfortable walking speed, and dual-task walking along a rectangle-shaped path to provide a wide range of strides at different gait speeds and cognitive loads. They were instructed to “walk at a comfortable pace,” “walk as fast as possible”, and “walk while performing the Word Generation List (WGL) test”, respectively.

Real-world Gait Analysis and Selected Digital Variable Definitions

The process for data collection and analysis is depicted in Figure 9. Patients were asked to wear one sensor on each ankle during daytime for 3 months from the baseline visit and 1 to 3 months after the 1-year visit (according to a protocol amendment version 5.0).

At the end of each recording period, raw data were analysed using Sysnav’s proprietary algorithms, which were specifically developed to analyse ambulation from the daily-living data collected by the wDHT device, ActiMyo®.

The algorithms detected individual strides and reconstructed the trajectory of the ankle from raw data (European Medicines Agency, n.d.-c; Michaud et al., 2024) from which multiple metrics are derived including stride length and stride velocity. Individual strides were grouped into walking episodes as periods of continuous walking without any time gap between two successive strides exceeding 15 seconds. At the walking-episode level, additional variables were computed, such as walking episode length, defined as the sum of the lengths of the individual strides composing the episode.

To establish a surrogate for maximal ambulation speed, as assessed in the T25FW, and maximal walking distance, as assessed in the EDSS, we focused on stride velocity and walking episode length, as these variables are clinically relevant in MS. Stride velocity and walking episode length were computed for each stride and each walking episode across the entire recording period (i.e., one month in this study) and then aggregated to generate distributions for each variable over the full recording period. From the distribution of these variables, we computed various percentiles (50th, 80th, 85th, 90th, 95th, 99th). We selected high percentiles to reflect maximal daily-living performance, while avoiding very high percentiles, as these are computed from a small number of strides or

walking bouts, which may have introduced variability in derived metrics. Our choice of centile was guided by the combined evaluation of reliability (ICC) and responsiveness (SRM) across percentiles. For maximal ambulation speed, we verified that the 95th percentile, the centile of stride velocity selected for qualification as a primary endpoint in DMD, was also a suitable choice for MS. For maximal walking distance, we selected a centile by balancing the goal of representing the top performance while limiting variability. The detailed results supporting the selection of the stride-velocity and walking-distance percentiles are provided in Figure 10.

As a result, we calculated the SV95C as an indicator of peak ambulation ability, defined as the 95th percentile of all stride velocities recorded during one month of daily living. Similarly, we calculated the walking distance 90th percentile (WD90C), as the 90th percentile of walking episode lengths recorded over the same period. In addition, overall physical activity was quantified as the number of strides per hour, calculated as the ratio between the total number of strides performed by the patient and the total recording duration with the wDHT over one month.

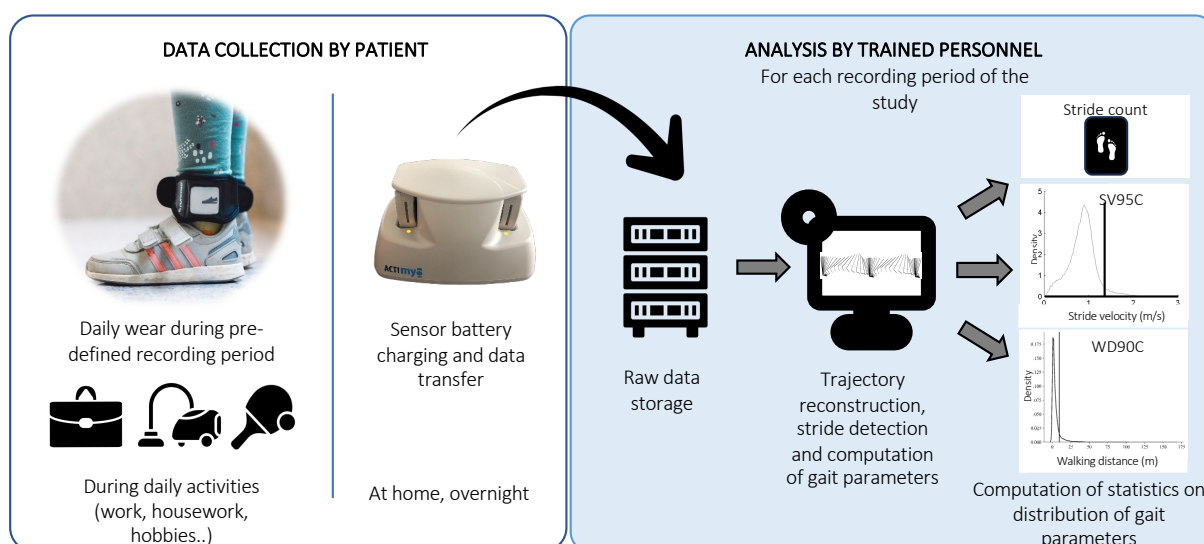


Figure 9. Data collection and analysis with the wDHT. Abbreviations: stride velocity 95th centile (SV95C), walking distance 90th centile (WD90C).

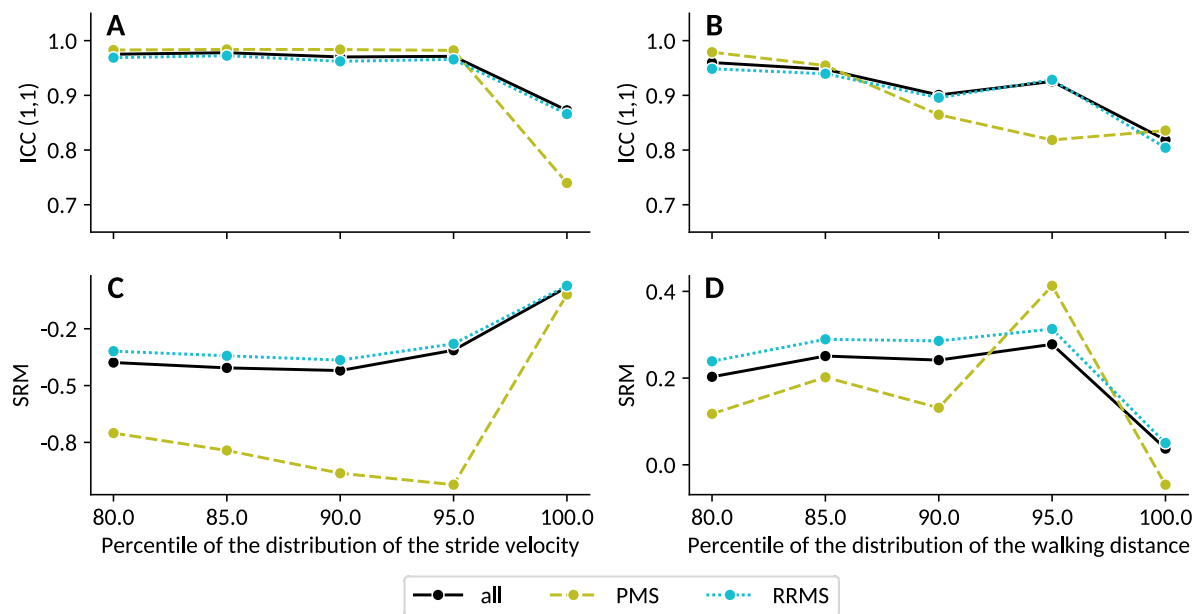


Figure 10. ICCs and SRMs across percentiles of stride velocity (A, C) and walking distance (B, D). *Abbreviations: intraclass correlation coefficients (ICC), standardised response means (SRM).*

Statistical Analysis

Statistical analyses were performed using Python (version 3.11). Population characteristics were analysed using descriptive statistics. Continuous and categorical clinical variables were compared between the populations of both studies, using the Wilcoxon rank-sum test and the chi-square test of independence, respectively.

ActiMS Controlled Environment Study: Analytical Validation

Analytical validation evaluates the performance of sensor technology and the data it produces at the sample level, based on a predefined set of criteria (Goldsack et al., 2020). SV95C relies on the ability of the wDHT to correctly detect strides and accurately estimate stride velocity in this population and in conditions representative of daily living. WD90C relies on the ability of the wDHT to detect strides correctly and accurately measure stride length.

The accuracy of the stride detection system was validated using manual annotations of strides. Manual labelling was performed by two skilled and trained engineers using LabelStudio, an interface displaying the wDHT sensor raw signals along axes relevant to gait detection. Joint review of the manual stride annotations was done with discussion to reach a consensus if necessary. Comparison between the manual annotations and outputs of the wDHT algorithm allowed to categorise each detected stride as a true positive (TP; correctly detected stride), false positive (FP; stride detected by the algorithm when none occurred), or false negative (FN; missed stride that was present in the manual annotation). After pooling data from both the left and right sides, per exercise and across all exercises, the analytical performance of the stride detection algorithm on MS patients was evaluated using the total number of true positive (TP), false positive (FP), false negative (FN), the precision, and the recall.

The precision of stride detection corresponds to the ratio of well-detected strides (total number of true positives strides) among all the detected strides (total number of true positive and false positive strides). It was evaluated using the following formula:

$$P = \frac{TP}{TP+FP}$$

Recall of stride detection corresponds to the ratio of well-detected strides (total number of true positive strides) among all the existing strides (total number of true positives and false negatives strides). It was evaluated using the formula:

$$R = \frac{TP}{TP+FN}$$

Validation of the accuracy of the system to measure stride velocity and length was performed against a gold standard reference (optical motion capture system, Mocap), after synchronisation of the Mocap and the wDHT data. For each individual stride, the error in the wDHT-estimated stride length or velocity was computed as the difference between the reference estimate and the wDHT estimate. The error was evaluated only for strides whose trajectories were captured by the Mocap system. Errors in wDHT-estimated stride length and stride velocity were evaluated using Bland-Altman analyses adapted for repeated measures to account for the non-independence of multiple strides originating from the same participant (Parker et al., 2020). In addition, quantitative metrics were computed, including the mean absolute error and the SD of the absolute error, defined respectively as the mean and SD of the absolute differences between wDHT and reference estimates. The mean relative absolute error was calculated as the mean absolute error divided by the corresponding reference estimate. Agreement between the Mocap and wDHT measurements was assessed using the ICC (1,1). The association between clinical variables (age, EDSS, height or body mass index) and the stride length or stride velocity error was graphically assessed. All analyses were performed by pooling strides from both the right and left sides.

Analyses were not stratified by disease phenotype (relapsing-remitting (RRMS) vs progressive MS (PMS)), as the study was not sufficiently powered to support reliable subgroup comparisons.

Longitudinal ActiMS Study in Daily Living Conditions

Each analysis was conducted using established statistical methods, allowing direct comparison with traditional clinical endpoints while accounting for the unique characteristics of digital outcomes.

Descriptive statistics were used to summarise population characteristics. Continuous clinical variables were compared between the baseline cohort and participants who withdrew from the study using the Wilcoxon rank-sum test. Categorical variables were compared between groups using the chi-square test of independence.

The minimal recording duration (MRD) was defined as the minimum amount of recording time required within a recording period to reliably compute digital metrics from the raw data. The optimal recording duration (ORD) was defined to inform power calculations and support the design of future clinical trials, including decisions on

recording-period length and participant compliance targets. To determine these two thresholds, we assessed the stability and reliability of the digital variables by calculating ICC [1,1] between pairs of consecutive recording periods with varying durations. MRD and ORD were operationally defined as the recording durations required to achieve ICC (1,1) values of 0.8 and 0.9, respectively. These thresholds therefore represent the minimum amount of raw data required to obtain stable and reproducible digital variables.

After evaluating the ORD and MRD, compliance was analysed for baseline and longitudinal data based on these definitions.

For the data analysis, we decided to evaluate the digital variables in periods of exactly one month from the start of the baseline period and the 1-year period. Moreover, to have one digital variable estimation per patient (as patients wore two sensors leading to two estimations), we chose the digital variable estimation from the ankle with the most strides during the baseline period.

Reliability was assessed at baseline using the ICC (2,1), which quantifies the consistency of measurements across different time periods. ICC (2,1) was calculated based on two consecutive 1-month measurement periods of the baseline recording period. This approach allowed us to determine the reliability of a single measurement over a month-long period. ICC values were interpreted as follows:

- < 0.50: poor reliability
- 0.50–0.79: moderate reliability
- 0.80–0.89: good reliability
- > 0.90: excellent reliability

The standard error of measurement (SEM), which reflects intra-patient variability, was calculated.

The distribution of all outcome variables was assessed using the Kolmogorov–Smirnov test for normality. This evaluation revealed heterogeneous distributional properties across outcomes. Specifically, the number of strides per hour, SV95C, EDSS, MSWS-12, MFIS, and MSIS-29 did not significantly deviate from normality, whereas WD90C, 9HPT, 25FW, the Berg Balance Scale, FAB, MMSE, and GLTEQ showed significant deviation from normality. Given this heterogeneity and the limited sample size for several outcomes, apparent normality was interpreted with caution. To ensure a conservative, consistent, and robust analytical strategy across all outcomes, non-parametric methods were therefore retained for all analyses.

Convergent and divergent validity of the digital metrics was evaluated by examining their correlation with traditional clinical endpoints assessing related and unrelated constructs at baseline using Spearman's rank correlation coefficient. Correlation coefficients were interpreted as follows:

- < 0.20: very weak correlation
- 0.20 – 0.40: weak correlation
- 0.40 – 0.60: moderate correlation
- 0.60 – 0.80: strong correlation
- > 0.80: very strong correlation

To account for multiple comparisons and reduce the risk of Type I errors, we applied a Bonferroni correction ($\alpha'=\alpha/m$). Given that multiple statistical tests were conducted, the standard significance level ($\alpha=0.05$) was adjusted by dividing it by the number of tests performed ($m=30$). This narrower threshold ($\alpha'=0.002$) reduces the likelihood that significant correlations represent random findings.

For known-group validity, we assessed whether the digital metrics could differentiate between groups with varying levels of disability at baseline. The study population was divided into three subgroups based on the EDSS:

EDSS $\leq$ 2: patients with no deficits

2 < EDSS < 4: patients with deficits but no gait disorder

EDSS $\geq$ 4: patients able to walk with limitations

Differences between groups were analysed using the Wilcoxon rank-sum test, a non-parametric alternative to the t-test that does not assume normality.

Longitudinal changes in digital and clinical metrics were assessed over a 1-year period. To account for potential non-normality and small sample sizes, we used the Wilcoxon signed-rank test, which is a non-parametric test for paired data. This analysis was conducted across the entire population and within the PMS and RRMS subgroups. As a post hoc analysis, we studied the correlation between SV95C and the MSWS-12, a patient-reported outcome that evaluates walking ability. Additionally, we investigated whether SV95C could distinguish between patients who experienced significant worsening, defined as a $\geq$ 4-point decline in MSWS-12, and those who did not.

IV. RESULTS

Population

Participant flow through the study is summarised in Figure 11. The baseline demographic and disease-related information of the study population are shown in Table 9. A total of 21 and 78 participants were recruited into the controlled environment and longitudinal studies, respectively. Nineteen patients who participated in the controlled environment study were also included in the daily living study. Seventeen patients with RRMS (aged 23-64 years), including 12 women, did not attend a follow-up visit. Reasons for withdrawal are detailed in Figure 11. As shown in Table 9, there were no significant differences in baseline characteristics between the populations of the two studies. In the daily living study, there were no significant differences between participants who withdrew and the overall study population with respect to age, gender, height, body mass index (BMI), age at first clinical manifestation, disease course, EDSS scores, T25FW, 9HPT (right and left), BBS, GLTEQ, MSWS-12, MFIS, or MSIS-29 ($p = 0.52, 0.37, 0.87, 0.36, 0.3, 0.07, 0.73, 0.93, 0.28, 0.7, 0.83, 0.21, 0.58, 0.64, \text{ and } 0.99$ respectively).

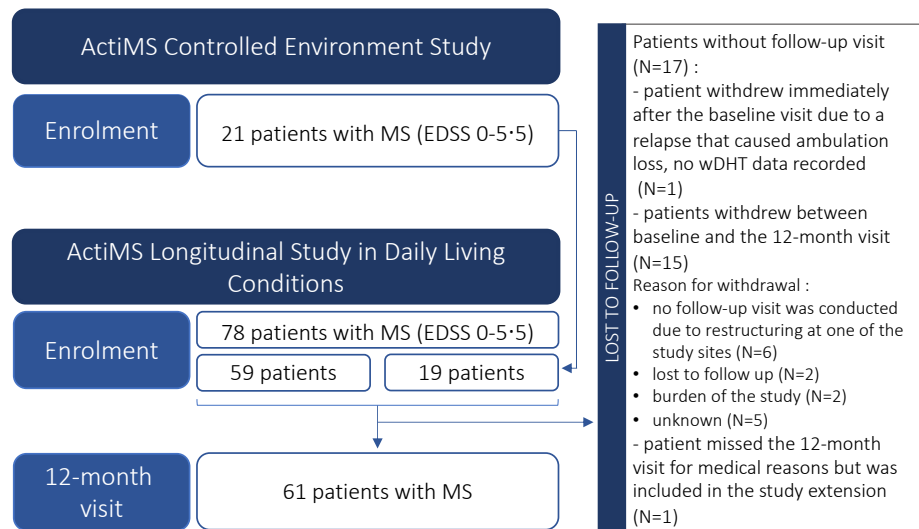


Figure 11. Diagram illustrating the flow of participants in both studies. *Abbreviations: Expanded Disability Status Scale (EDSS), multiple sclerosis (MS), wearable digital health technology (wDHT).*

		Controlled Environment Study			Longitudinal Daily Living Study			Overall population comparison (p-value)
		Total	RRMS	PMS	Total	RRMS	PMS (primary/ secondary)	
Number of patients		21	18	3	78	61	17 (9/8)	NA
Age (years): median (IQR) [range]		39 (34–54) [23–62]	38.5 (34.5–52.7) [23–62]	51 (42–56) [33–61]	48.5 (38.2–55) [23–64]	43 (37–54) [23–64]	55 (51–58) [33–62]	0.16 ns
Height (centimetres) : mean $\pm$ SD [range]		172.4 $\pm$ 11.7 [152.5– 189.8]	172.9 $\pm$ 9.7 [152.5– 189.8]	169.5 $\pm$ 16 [153.2– 185.2]	170.9 $\pm$ 9.8 [151–189.8]	170.8 $\pm$ 9.7 [151–189.8]	171.6 $\pm$ 10.7 [151–185.2]	0.50 ns
BMI (kg/m ²): mean $\pm$ SD [range]		27.3 $\pm$ 4.2 [21.4–36.2]	27.1 $\pm$ 3.9 [21.4–36.2]	28.3 $\pm$ 6.3 [21.8–34.5]	26.6 $\pm$ 4.8 [18.6–45]	26.7 $\pm$ 4.9 [18.7–45]	26.3 $\pm$ 4.9 [18.6–35.2]	0.43 ns
Sex: female (%)		12 (54.5)	11 (61.1)	1 (33.3)	43 (55.1)	37 (60.7)	6 (35.3)	1 ns
EDSS: mean $\pm$ SD [range]		2.6 $\pm$ 1.3 [1.5–5.5]	2.2 $\pm$ 1 [1.5–5.5]	4.7 $\pm$ 1 [3.5–5.5]	3 $\pm$ 1.4 [0–5.5]	2.7 $\pm$ 1.3 [0–5.5]	4.1 $\pm$ 1.1 [1.5–5.5]	0.25 ns
T25FW (s): mean $\pm$ SD [range]		5.3 $\pm$ 2.3 [3.1–13.7]	4.7 $\pm$ 1.4 [3.1–9.6]	5.4 $\pm$ 4.8 [5.4–13.7]	6.5 $\pm$ 6.7 [2.8–60]	5.2 $\pm$ 2.2 [2.8–17.5]	11.2 $\pm$ 13 [4.3–60]	0.28 ns
9HPT right side (s): mean $\pm$ SD [range]		21.8 $\pm$ 6.0 [13.8–37.3]	20.4 $\pm$ 3.7 [13.8–27.3]	30.4 $\pm$ 10.8 [18–37.3]	24.8 $\pm$ 14.9 [15.5–135.2]	23.4 $\pm$ 15.5 [15.5–135.2]	29.6 $\pm$ 11.4 [18.3–59.9]	0.41 ns
9HPT left side (s): mean $\pm$ SD [range]		22.8 $\pm$ 5.8 [15.4–35.0]	21.5 $\pm$ 4.5 [15.4–32.5]	30.8 $\pm$ 7.3 [22.4–35.0]	24.1 $\pm$ 7.4 [16.0–60.6]	23.0 $\pm$ 6.1 [16.0–46.5]	27.8 $\pm$ 10.2 [19.8–60.6]	0.50 ns
6MWT (meters): mean $\pm$ SD [range]		NA	NA	NA	448.8 $\pm$ 139.5 [147.5–774]	478.2 $\pm$ 130.1 [200–774]	329 $\pm$ 112.9 [147.5–479]	NA
BBS: mean $\pm$ SD [range]		NA	NA	NA	51.9 $\pm$ 6.3 [18–56]	53.4 $\pm$ 4.0 [36–56]	46.2 $\pm$ 9.5 [18–56]	NA
GLTEQ: mean $\pm$ SD [range]		20.5 $\pm$ 18.2 [0–63]	21.7 $\pm$ 17.7 [0–63]	13.3 $\pm$ 23.1 [0–40]	25.0 $\pm$ 26.3 [0–140.0]	27.8 $\pm$ 28.4 [0–140.0]	14.8 $\pm$ 12.6 [0–40]	0.71 ns

MSWS-12:	24.4 ± 14.1	20.8 ± 11.1	46.0 ± 11.3	27.8 ± 13.2	24.9 ± 12.4	37.9 ± 11.2	0.20 ns
mean ± SD	[12–59]	[12–44]	[39–59]	[12–60]	[12–60]	[17–59]	
[range]							
MFIS: mean ± SD	32.9 ± 21.8	30.7 ± 21.1	46.3 ± 25.7	37 ± 21.9	33.8 ± 21.9	48.5 ± 19.0	0.47 ns
[range]	[0–65]	[0–65]	[17–65]	[0–80]	[0–80]	[10–74]	
MSIS-29:	59.8 ± 20.4	57.3 ± 20.1	74.7 ± 19.0	62.0 ± 22.0	61.3 ± 21.8	64.8 ± 23.5	0.77 ns
mean ± SD	[30–94]	[30–90]	[56–94]	[30–129]	[30–129]	[41–111]	
[range]							

Table 9. Population characteristics. Abbreviations: 6-minute walking test (6MWT), 9-Hole Peg Test (9HPT), Berg Balance Scale (BBS), body mass index (BMI), Expanded Disability Status Scale (EDSS), Godin Leisure Time Exercise Questionnaire (GLTEQ), interquartile range (IQR), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Impact Scale (MSIS-29), 12-item Multiple Sclerosis Walking Scale (MSWS-12), not applicable (NA), progressive multiple sclerosis (PMS), relapsing-remitting multiple sclerosis (RRMS), standard deviation (SD), Timed 25 Foot Walk (T25FW).

ActiMS Controlled Environment Study

Analytical Validation

The results of the analytical validation of stride detection and stride velocity and length estimation are listed in Table 10. The performance of stride detection was excellent in patients with MS, as indicated by precision (near 1 for all exercises) and recall (0.96 for all exercises).

Due to the setup of the controlled environment (limited coverage area of the camera), the availability of strides was lower for the Mocap than for the wDHT. Results of the analytical validation of stride velocity and length are presented in Figures 12 and 13. The wDHT-derived stride velocity and length were accurate (mean absolute error 0.019 m/s and 0.022 m, respectively) and precise (SD of the absolute error of 0.019 m/s and 0.023 m respectively) on both ankles and across all exercises (Table 10).

The mean relative absolute error was low for both stride velocity and stride length (2.1–2.7%), indicating a small proportional error over the full range of measured values. Agreement between wDHT and Mocap was excellent across all exercises. ICC values ranged from 0.996 to 0.998 for stride velocity estimation and from 0.992 to 0.996 for stride length estimation, demonstrating near-perfect agreement (Table 10).

As demonstrated in Figure 12 by the lines at ± 1.96 SD, the length and velocity of 95% of the strides are quantified with errors below 7 cm and 6 cm/s, respectively. Based on visual inspection, no systematic relationship was observed between stride velocity or stride length errors and their corresponding measured values.

As illustrated in Figure 13, the mean errors in stride velocity and length were similarly distributed across all exercises. No clear trends or dependencies were observed between clinical variables (age, EDSS, height, and BMI) and the mean errors in stride velocity and stride length per patient.

		All exercises	Fast walk	Comfortable walk	Dual-task walk
Stride detection	TP (number of strides)	10448	3160	3629	3659
	FP (number of strides)	6	2	2	2
	FN (number of strides)	434	120	162	152
	Precision	0.999	0.999	0.999	0.999
	Recall	0.960	0.963	0.957	0.960
Stride velocity estimation	Stride count (common to Mocap and wDHT)	3808	1065	1329	1414
	Mean absolute error (m/s)	0.019	0.020	0.022	0.016
	Mean relative error (%)	2.305	2.103	2.660	2.123
	SD absolute error (m/s)	0.019	0.020	0.022	0.014
	ICC(1,1) agreement	0.998	0.998	0.996	0.998
Stride length estimation	Stride count (common to Mocap and wDHT)	3808	1065	1329	1414
	Mean absolute error (m)	0.022	0.022	0.026	0.020
	Mean relative error (%)	2.305	2.103	2.660	2.123
	SD absolute error (m)	0.023	0.021	0.028	0.019
	ICC(1,1) agreement	0.995	0.996	0.992	0.996

Table 10. Metrics for stride detection, stride velocity and length estimation per exercise. *Abbreviations: false negative (FN), false positive (FP), intraclass correlation coefficient (ICC), motion capture (Mocap), standard deviation (SD), true positive (TP), wearable digital health technology (wDHT).*

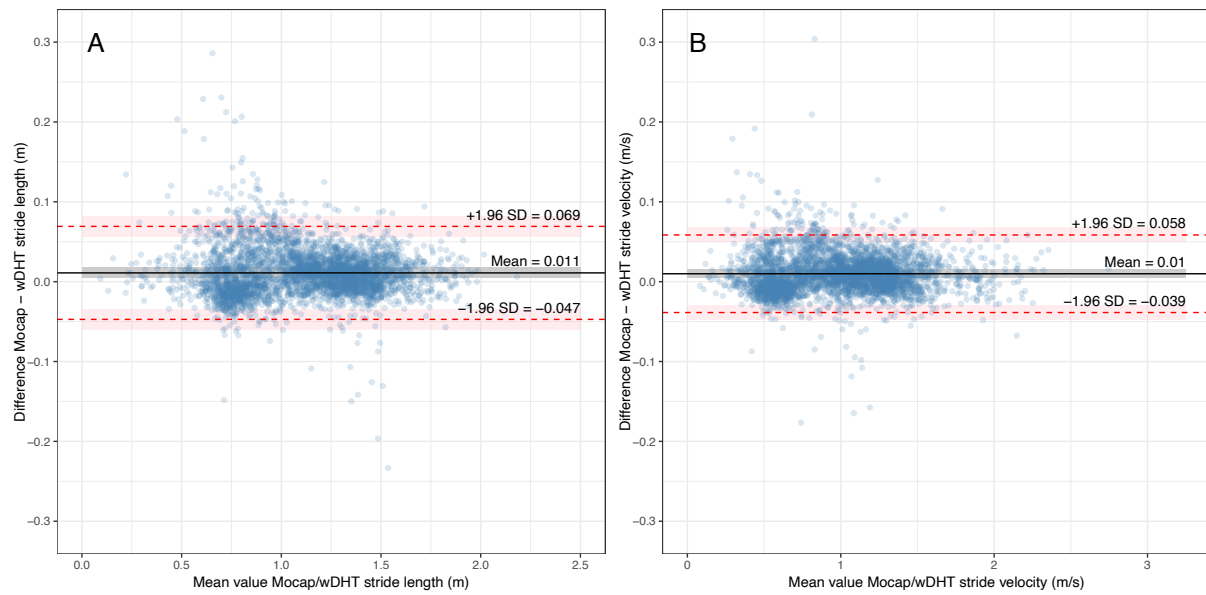


Figure 12. Bland-Altman plot showing the error in stride length (A) and velocity (B) for individual strides, as a function of the mean value of each variable. Black line is the mean error for all strides, and red dashed lines indicate the limits of agreement. Grey shaded area indicates the 95% confidence interval around the mean error and red shaded areas represent the 95% confidence intervals of the limits of agreement. Abbreviations: motion capture (Mocap), standard deviation (SD), wearable digital health technology (wDHT).

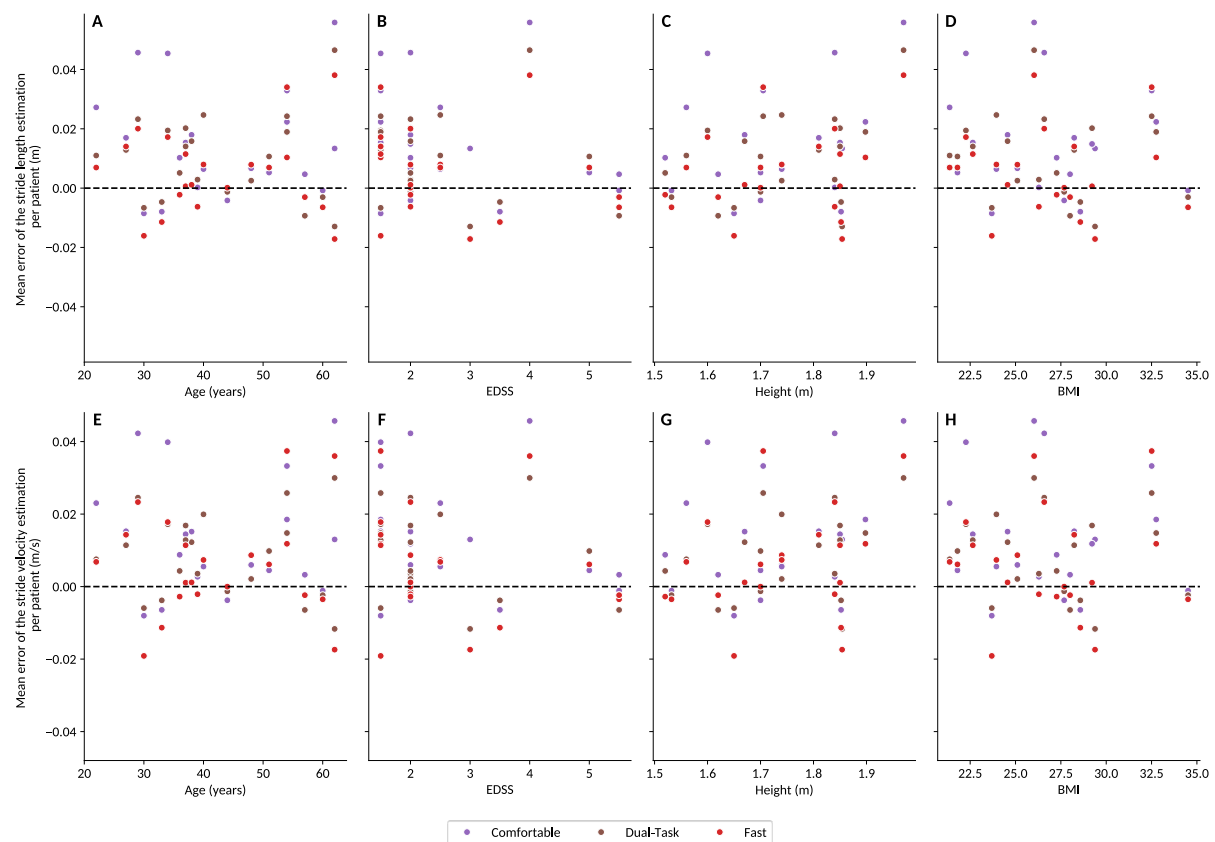


Figure 13. Impact of age, EDSS, height, and BMI on the mean error of stride length (A, B, C, and D) and velocity (E, F, G, and H). Abbreviations: body mass index (BMI), Expanded Disability Status Scale (EDSS).

Longitudinal Study in Daily Living Conditions

Clinical Data Availability

At baseline, MSIS-29 assessments were missing because this measure was added later through a protocol amendment (n=16), with an additional four cases resulting from site oversight. The 6MWT was also missing for 16 participants for the same amendment-related reason. At the 12-month visit, missing data were limited to four participants who did not complete any follow-up clinical assessments due to site restructuring, along with a small number of isolated missing values for the MSWS-12 (n=3) and MFIS total score (n=1) related to site oversight. Overall, only a small proportion of clinical outcome measures were missing across both visits.

wDHT wear time

The comparison of multiple ICCs, computed using two consecutive recording periods of variable lengths, enabled the validation of the MRD and ORD in the MS population and is detailed in Figure 14. This demonstrates that MRD and ORD can be defined as 50 h and 180 h, respectively.

The baseline and 1-year wear-time data (<MRD, MDR-ORD, and >ORD) are presented in Table 11. In total, 98.7% and 91.5% of patients provided sufficient data for analysis (>50h) at baseline and 1 year, respectively.

Period	Baseline	1 year
<50 hours: n (%)	1 (1.3)	5 (8.5)
50–180 hours: n (%)	13 (16.9)	6 (10.2)
>180 hours: n (%)	63 (81.8)	48 (81.4)

Table 11. Sensor wear time (number and percentage of participants by recording duration).

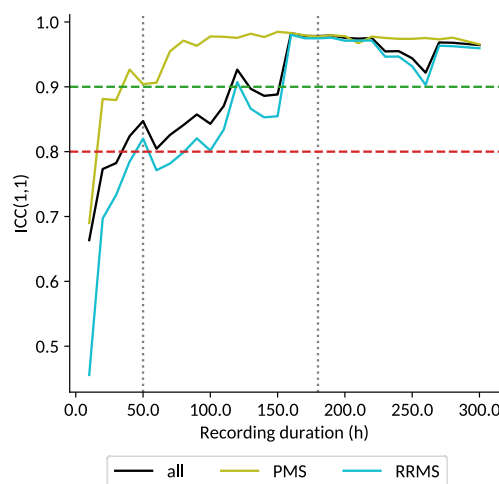


Figure 14. ICCs of the SV95C as a function of the length of the two consecutive recording periods used to compute them. Abbreviations: intraclass correlation coefficient (ICC), progressive multiple sclerosis (PMS), relapsing–remitting multiple sclerosis (RRMS).

Reliability

Cross-sectional analysis demonstrated the high reliability of SV95C (ICC (2,1) = 0.97, SEM=0.06, n=71), number of strides per hour (ICC (2,1) = 0.91, SEM=25.92, n=75) and WD90C (ICC (2,1) = 0.90, SEM=8.02, n=73). The reliability of the different digital metrics was not (for SV95C) or moderately (for WD90C) dependent on their magnitude, as shown in Figure 15. Reliability remained good to excellent across all digital metrics and when RRMS and PMS groups were analysed separately, with ICC(2,1) values ranging from 0.86 to 0.98. The highest reliability was observed for SV95C, with ICC(2,1) values of 0.96 and 0.98 in the RRMS and PMS groups, respectively.

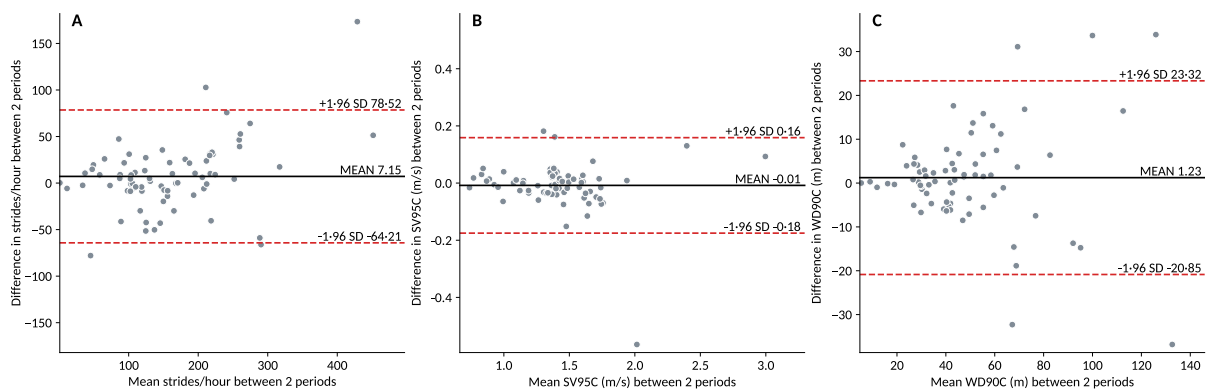


Figure 15. Bland-Altman plot showing the variation between 2 consecutive 1-month periods for each digital variable, as a function of their mean values. *Abbreviations: standard deviation (SD), stride velocity 95th centile (SV95C), walking distance 90th centile (WD90C).*

Known Group Validity:

SV95C and WD90C were able to differentiate between all three EDSS subgroups. Figure 16 presents box plots for each digital metric with three EDSS subgroups.

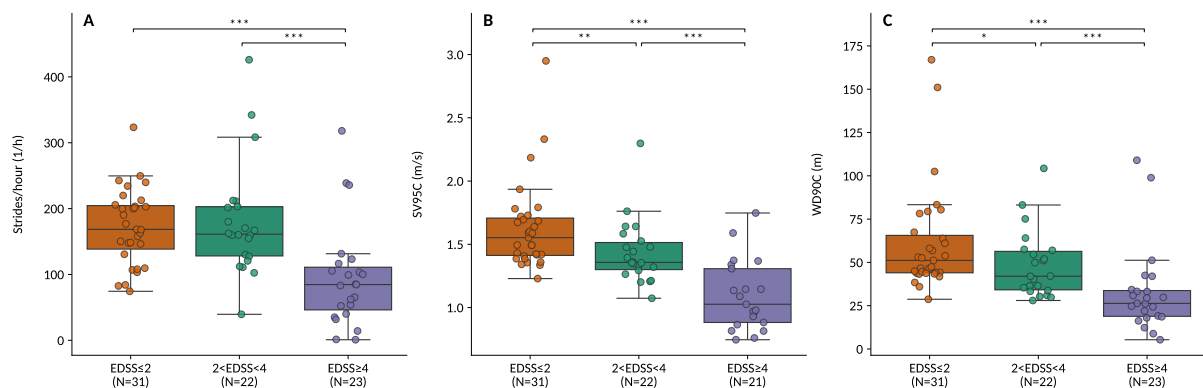


Figure 16. Digital outcome measures by level of disability ($p<0.05^*$, $p<0.01^{**}$, $p<0.001^{***}$). *Abbreviations: Expanded Disability Status Scale (EDSS), stride velocity 95th centile (SV95C), walking distance 90th centile (WD90C).*

Convergent and Divergent Validity:

All digital metrics demonstrated moderate to strong correlations with EDSS, T25FW, BBS, MSWS-12, and GLTEQ (Figure 17). These relationships remained significant after Bonferroni correction ($p < 0.003$). Correlations with outcomes related to motor function but not directly reflecting lower-limb function (MFIS and 9HPT) were generally weaker but remained statistically significant for WD95C ($p = 0.285$, $p < 0.05$ and $p = 0.327$, $p < 0.01$, respectively) and SV95C ($p = 0.326$, $p < 0.01$ and $p = 0.521$, $p < 0.01$, respectively). The digital mobility metrics showed no meaningful correlation with measures not primarily related to mobility (MMSE and FAB), supporting the divergent validity of the digital mobility metrics (Figure 17). The results of the correlations between digital metrics and traditional clinical outcomes stratified by disease group (RRMS and PMS) are provided in Figure 18.

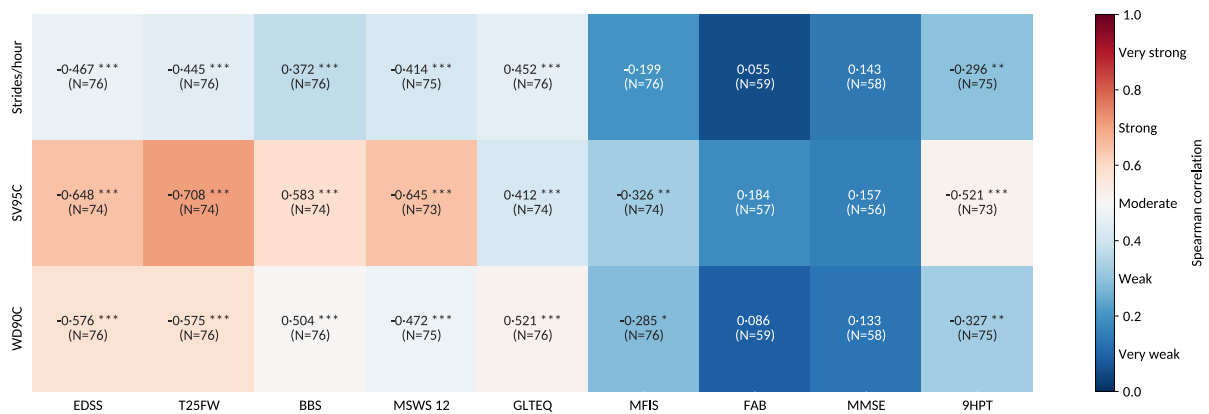


Figure 17. Correlations between digital and clinical variables ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$). Abbreviations: Berg Balance Scale (BBS), Expanded Disability Status Scale (EDSS), Frontal Assessment Battery (FAB), Godin Leisure Time Exercise Questionnaire (GLTEQ), Mini-Mental State Examination (MMSE), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Walking Scale–12 (MSWS-12), 9-Hole Peg Test (9HPT), stride velocity 95th centile (SV95C), Timed 25-Foot Walk (T25FW), walking distance 90th centile (WD90C).

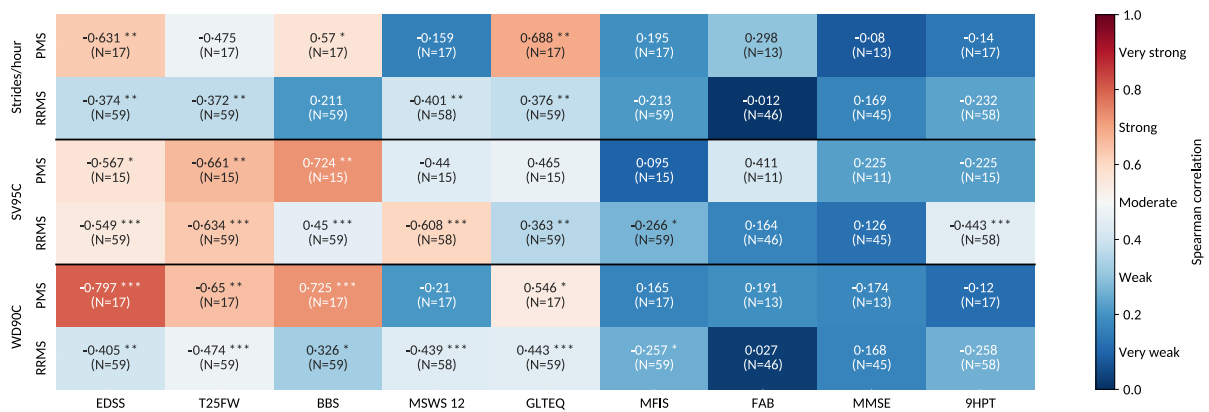


Figure 18. Correlations between digital and clinical variables by disease group (RRMS and PMS) ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$). Abbreviations: Berg Balance Scale (BBS), Expanded Disability Status Scale (EDSS), Frontal Assessment Battery (FAB), Godin Leisure Time Exercise Questionnaire (GLTEQ), Mini-Mental State Examination (MMSE), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Walking Scale–12 (MSWS-12), 9-Hole Peg Test (9HPT), progressive multiple sclerosis (PMS), relapsing–remitting multiple sclerosis (RRMS), stride velocity 95th centile (SV95C), Timed 25-Foot Walk (T25FW), walking distance 90th centile (WD90C).

Sensitivity to Change

SV95C demonstrated a statistically significant decline over 12 months in both the PMS and RRMS populations ($p = 0.006$ and $p = 0.049$, respectively), whereas EDSS showed a significant change only in the PMS population ($p = 0.01$), as illustrated in Figure 19. T25FW showed a statistically significant improvement in the RRMS group over 1 year (mean change: 0.63 seconds, $p = 0.03$); however, the magnitude of this improvement was minimal and may not be clinically meaningful. In the PMS group, no significant change was observed in T25FW. We did not observe any changes in pharmacological treatment or physical activity levels (as measured by the GLTEQ) that could account for the increases in T25FW performance in RRMS. For SV95C, the SRMs for changes at 12 months were -0.936 for PMS and -0.316 for RRMS. For EDSS, the SRM for changes at 12 months in the PMS group was 0.716.

In a post-hoc analysis, the correlations between changes in MSWS-12 and SV95C did not reach statistical significance in the overall population ($R = -0.27$, $p = 0.07$, $n = 47$), nor in the PMS ($R = -0.29$, $p = 0.31$, $n = 14$) or RRMS ($R = -0.24$, $p = 0.18$, $n = 33$) subpopulations. SV95C did not differentiate between patients who exhibited a significant decline in MSWS-12 (defined as an increase of 4 points) and those who did not.

In the two patients who experienced a relapse during the 1-year follow-up, SV95C decreased by 7 cm/s and 8 cm/s. WD90C and strides per hour also declined (-1.9 and -10.7 m, -39 and -78 strides, respectively). In these patients, EDSS increased by 0.5 and 1.0 point, MSWS-12 scores worsened significantly (+6 and +23 points, respectively), while T25FW showed no meaningful change.

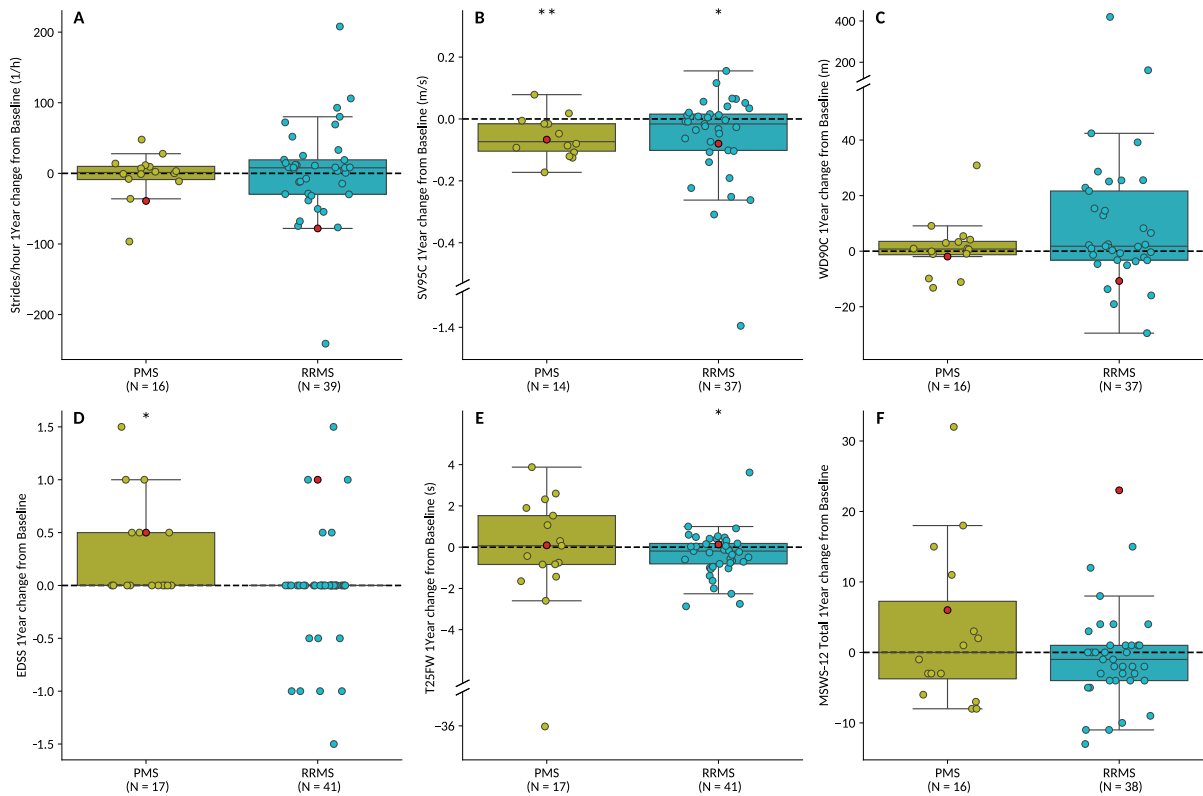


Figure 19. Box plots with change from baseline by subgroup (RRMS/PMS) for each digital and clinical outcome ($p < 0.05^*$, $p < 0.01^{**}$). The red dots represent patients who experienced a relapse during the 1-year follow-up. Abbreviations: Expanded Disability Status Scale (EDSS), Multiple Sclerosis Walking Scale–12 (MSWS-12), progressive multiple sclerosis (PMS), relapsing–remitting multiple sclerosis (RRMS), stride velocity 95th centile (SV95C), Timed 25-Foot Walk (T25FW), walking distance 90th centile (WD90C).

V. DISCUSSION

We demonstrate that a digital outcome based on individual stride-level data shows strong potential as a sensitive and reliable early measure of ambulation decline experienced by people with MS. In contrast to traditional approaches that rely on aggregated measures, such as mean step count, average daily walking speed, or walking-bout-level metrics, our method identifies and segments every stride to compute stride-specific velocity and stride length. This enables a percentile-based analysis of stride distributions. Some of the proposed digital metrics, such as SV95C, are based on stride-level detection, measurement, and on analysis of stride-level distributions. By contrast, metrics based on stride counts or walking-bout characteristics rely on aggregation approaches similar to those used in previous studies. By leveraging the full distribution of stride characteristics rather than average-based measures typically obtained from lower-back-mounted wearable sensors (Kirk et al., 2024), our approach offers a novel opportunity to detect subtle mobility impairments at an earlier stage.

The stride detection, as well as stride velocity and length measurements, of the wDHT demonstrated high accuracy, with significantly reduced errors compared with levels typically reported in publicly available data from other research-grade sensors (Banks et al., 2025; Kirk et al., 2024). The excellent reliability of SV95C (ICC of 0.97) observed in our study surpasses the reliability of outcomes that simply reflect overall patient activity, such as the

number of strides per hour and WD90C. Additionally, this level of reliability exceeded that of other gait-related outcome measures reported in the literature (Montalban et al., 2022), and is comparable to the reliability demonstrated during the EMA qualification of the same outcome in DMD (Servais et al., 2023) or in other neuromuscular diseases (Gidaro et al., 2022). We were able to quantify the annual decline in both RRMS and PMS, whereas EDSS showed a statistically significant decline only in the PMS subgroup. Although these results require confirmation in larger, independent cohorts, they suggest that SV95C could be used to detect disability progression in PMS and RRMS populations. This potential is particularly important, as sensitivity is a key determinant of statistical power in efficacy trials.

We computed three digital outcomes representing distinct aspects of gait impairment, all of which showed good metric properties in MS. The number of strides per hour and maximal walking distance (WD90C) provide a continuous and granular measure of mobility, as suggested by the wide variability observed within the same EDSS level. In MS (Woelfle et al., 2023), few studies have demonstrated that step count may be partially sensitive to change. However, interpreting changes in these metrics remains challenging, as they can be significantly influenced by factors beyond disease progression, such as lifestyle, motivation, comorbidities, fatigue, and environmental conditions. Gait parameters, such as SV95C, may show lower variability driven by external factors and greater variability attributable to disease progression. This is reflected in its excellent reliability and strong sensitivity to change. This is consistent with observations in other diseases, where step count and cumulative activity metrics are less reliable and less sensitive to changes (Gidaro et al., 2022; Servais et al., 2023) than outcomes based on individual stride metrics such as SV95C.

Overall, these three digital outcomes (strides per hour, WD90C and SV95C) accurately reflect daily walking ability, correlate with gold standard measures, and distinguish between patients with different levels of disability. The most promising outcome (SV95C) appears to be more reliable, more discriminant, and more sensitive to decline than other digital outcomes.

Although promising, wDHT-based gait assessments in daily living are not yet the gold standard nor widely adopted. Some clinical trials in MS have already begun to use wDHT to provide outcome measures (Alexander et al., 2021), but the need for further validation of these outcomes and wDHT is urgent. Emerging guidance for evaluation of digital assessments (Goldsack et al., 2020) is essential to address the current lack of standardisation and result comparability, which currently prevents the integration of these innovative solutions into clinical trials. The implementation of such technology – beyond consumer-grade devices – in clinical practice is even more distant. Key challenges include addressing the burden on patients, as well as the accessibility and interpretability of the data for both clinicians and patients.

This study has several limitations that should be acknowledged. Despite the large volume of recorded data, the sample size was relatively limited, particularly within subgroups (RRMS/PMS), and particularly in the analytical validation cohort. As a result, the study was not powered to support formal subgroup analyses by sex or age, or site-stratified analyses. However, the data generated here provide a basis for future sample size calculations in

studies designed to confirm these findings and assess their generalisability. Future studies should include a larger representation of patients with PMS. In addition, recruitment was restricted to European centres and ambulant individuals, with limited ethnic diversity and representation of patients with high disability levels, which may further limit the generalisability of the findings. Longitudinal data are currently being collected in an independent cohort of similar size from a non-European population to address these limitations. Moreover, the study was initially designed as a 1-year investigation and was extended to a 3-year study, with recording periods every 6 months, to provide a more comprehensive assessment of disease progression over shorter intervals. Additionally, we observed a high dropout rate, along with a decline in adherence between the first and second recording periods. It is important to note that six of the 17 withdrawals were due to restructuring at one of the study sites. Although device-related withdrawals have rarely been reported, our data collection did not allow systematic determination of the exact reasons. To address potential device-related withdrawals and improve adherence, a new version of the wDHT has been developed to better meet patients' expectations regarding aesthetics and comfort. Additionally, comparison with age-matched healthy controls is essential to distinguish MS-related decline from normal ageing. Some normative data have been published (Poleur et al., 2021) but expanding the coverage of the adult population is necessary. Finally, we selected a short list of digital outcomes based on well-known concepts of interest in MS, a post hoc analysis could extend this list to explore new metrics and other concepts of interest. Future analyses may explore digital metrics to assess fatigability and upper limb function.

Nevertheless, this small-scale study demonstrated that individual stride detection using a valid and suitable wDHT in patients with MS exhibits key features, highlighting its practical potential as an early surrogate for ambulatory decline, a critical component of MS progression. Further research is essential to confirm these preliminary findings and to expand the potential applications of this technology. Efforts should prioritise the rigorous validation of digital outcome measures to assess ambulation in patients with MS, integrating these into regulatory frameworks. The next steps include validating these findings in an independent population and collecting age-matched normative data. Expanding data acquisition will help to establish meaningful thresholds for a decline in walking ability, whereas determining a meaningful threshold for improvement will represent a more challenging but crucial step towards validating a digital outcome: its integration into interventional trials as an exploratory endpoint.

VI. KEY INSIGHTS

The 95th percentile of stride velocity, derived from real-world, stride-level data, provides a valid, reliable, and sensitive digital outcome for detecting MS progression. It may serve as an early indicator of progression and support the accelerated evaluation of treatments targeting MS progression.

AMYOTROPHIC LATERAL SCLEROSIS

The findings presented in this chapter are the result of an international collaboration. Data collection is ongoing. The data cut-off for the analyses included in this manuscript is October 8, 2025. The full dataset will be published in 2026.

I. CLINICAL OVERVIEW

ALS is a progressive neurodegenerative disease characterised by motor neuron loss, leading to muscle weakness, loss of ambulation, and ultimately respiratory failure leading to death within, on average, three to five years after symptom onset (van Es et al., 2017).

Over the past two decades, substantial advances have been made in understanding the pathophysiology of ALS. However, the translation of this knowledge into effective treatments has been disappointing (Kiernan et al., 2021). Multiple factors contribute to the persistent challenge of developing efficacious ALS treatments including intrinsic disease features, including its complex and heterogeneous pathophysiology. Variability in the site of symptom onset, patterns and rates of disease progression, as well as the degree of upper motor neuron involvement further diminish the likelihood that a single, universal approach will be adequate for either treatment or the assessment of therapeutic efficacy (Goutman et al., 2022; Kiernan et al., 2021). In addition to disease complexity, the evaluation of therapeutic efficacy is challenged by the absence of validated biomarkers and robust clinical trial outcome (Van Den Berg et al., 2019), which further complicate the ability to determine whether an intervention is truly effective

ALS therapeutic development has largely relied on staff-administered functional rating scales. The ALSFRS-R is a semi-quantitative rating scale that uses multiple choice questions to evaluate several functions (e.g., walking, handwriting, speech, swallowing) and disease progression over time (Cedarbaum & Stambler, 1997). It has served as the primary outcome measure for years to assess drug efficacy in clinical trials with limited success (Paganoni et al., 2020, 2025). Although this measure broadly captures ALS-related impairment, it remains subjective and has limited sensitivity to detect subtle changes over time. Moreover, the aggregation of distinct functional domains into a single score introduces multidimensionality, complicating the interpretation of treatment effects (van Eijk et al., 2021). As a result, and in combination with other factors, clinical trials often require long durations and large sample sizes, a considerable challenge in such a rare and rapidly progressive disease.

Beyond the urgent need for more effective therapies, these factors highlight a critical unmet need for more sensitive, objective, and disease-relevant clinical outcome measures in ALS. Improved endpoints capable of capturing subtle functional changes and reflecting real-world patient's experience will be essential to accelerate

therapeutic development and increase the likelihood of identifying effective treatments for this devastating disease.

In contrast to questionnaire-based measures, outcomes derived from wDHTs are designed to capture a single disease domain, such as motor function, through objective, high-resolution measurements (Beswick et al., 2022). This targeted, objective, and passively collected approach may better capture domain-specific disease progression under ecologically valid conditions. Because these outcomes are not dependent on a patient's ability to perform prescribed tasks, they may support higher compliance and more consistent monitoring (Warmerdam et al., 2020). Their potentially greater sensitivity to change, together with their feasibility as alternative outcome measures, suggests that wDHT-based metrics could substantially reduce sample size requirements and trial duration (Rutkove et al., 2020; van Eijk et al., 2019).

Existing ALS studies using wDHT have primarily focused on physical activity or step-count metrics, demonstrating correlations between these measures and traditional clinical outcomes (Van Unnik et al., 2025). Two longitudinal studies have shown significant change in physical activity metrics over six months (Johnson et al., 2023), and improved progression tracking using multimodal home-based measurements (Rutkove et al., 2020). More advanced approaches, including multi-sensor ML models (Gupta et al., 2023), have outperformed the ALSFRS-R in sensitivity to change, discriminating between fast and slow progressors and predicting loss of ambulation (Gupta et al., 2023; van Unnik et al., 2024)

Despite their promising feasibility and acceptability, no digital outcome measure has yet achieved the level of validation required for regulatory use as a clinical trial endpoint. The extent to which these measures capture the full heterogeneity of ALS and reliably differentiate progression rates remains insufficiently understood. A consensus on which digital concept or metric best reflects ALS disease progression is still lacking, and operational considerations (e.g., optimal monitoring schemes) remain inadequately defined.

II. AIM

This project aims to evaluate the feasibility of assessing ambulation in ALS using wDHTs and to determine the precision, reliability, construct validity and sensitivity to change of three digital mobility measures, number of strides per hour, SV95C, and peak walking distance (walking distance 95th centile, WD95C), which respectively quantify total ambulation activity, peak ambulatory capacity, and endurance.

III. METHODS

Study Design and Population

Analytical Validation

We are conducting a monocentric cross-sectional study, “Mocap,” initiated in August 2022, to validate the performance of a wDHT in detecting strides and quantifying gait features in participants with disorders affecting motor function, including ALS at Citadelle Hospital in Liège, Belgium.

Longitudinal Data Acquisition

We are conducting and aggregating data from three one-year, longitudinal studies in two centres: NMRC in Belgium (NCT04882904, NCT06228001) and Massachusetts General Hospital (MGH) in the United States. Eligible participants for these analyses were ambulant patient over 18 years old with possible, probable or definite ALS, as defined by the El Escorial criteria, with a disease onset within the past five years. The exclusion criteria were significant cognitive disorders, other previous or current diseases that could impact the patient's current motor function, and recent surgery or trauma.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval for the protocols was obtained from Ethic Committees of all participating sites. After receiving information about the study, patients provided their written informed consent.

All studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Data Collection

Analytical Validation

Performance of the Existing Algorithm and Algorithm Refinement

Participants performed a 6MWT while wearing the sensors during the baseline visit of the longitudinal study. This assessment was used to evaluate the performance of the stride-detection algorithm, which has previously been validated in other clinical conditions (European Medicines Agency, n.d.-c; Michaud et al., 2024).

When applied to our cohort, the algorithm exhibited false-negative stride detections in participants with severe weakness, resulting in an underestimation of the number of detected strides. These findings motivated targeted refinements of the algorithm to improve step detection sensitivity in individuals with marked weakness, reduced foot-clearance amplitude, slower and more irregular gait patterns, and shorter walking bouts.

More specifically, the initial stride-detection algorithm relied on a first-stage identification of walking windows based on frequency-domain analysis of inertial signals. Given that normal gait exhibits a well-defined and periodic pattern, frequency-based criteria were used to detect segments likely to contain walking. However, in participants

with severely impaired gait, such as individuals with advanced ALS, these periodic patterns were often disrupted, leading to a failure in identifying walking windows and, consequently, an absence of detected strides.

To address this limitation, the frequency-based walking window detection was replaced with a more general movement-based detection approach. This modification enabled the identification of candidate movement segments even when gait patterns were highly irregular or distorted. The subsequent stages of the algorithm, which are responsible for detecting individual strides within these segments and extracting their characteristics, remained unchanged.

The refinement process included three main phases. First, the sources of stride-detection errors were identified using 6MWT data, where short recordings allowed for reliable ground-truth annotation. Second, the stride-detection algorithm was modified to address these limitations. Third, the updated algorithm was verified and validated using 6MWT data. Finally, the refined algorithm was further validated within the analytical validation study described above.

Analytical Validation of the Refined Algorithm

Participants were equipped with a wDHT device (ActiMyo®, Sysnav, Vernon, France) and Mocap markers (OptiTrack®, NaturalPoint, Oregon, U.S.A.) placed on both ankles, with the markers attached directly to the wDHT. The walking assessment consisted of six laps along a figure-8 path (3 × 7 meters), covering an approximate total distance of 106 meters, under three different conditions: normal walking, fast walking, and perturbed walking (dual-task condition involving the WGL test). Participants were instructed to “walk at a comfortable pace,” “walk as fast as you can,” and “walk while performing the WGL test,” respectively. Stride detection, as well as the accuracy of stride length and velocity, were then compared between the two systems.

Longitudinal Data Acquisition

Clinical Evaluation

Clinical outcomes included the ALSFRS-R, Medical Research Council Scale (MRC) for muscle strength and the 6MWT, which were collected every three months. Clinical data were collected on both paper and electronic case report form.

Real-world Gait Analysis

Participants wore ActiMyo® or Syde® sensors on the most affected ankle and wrist for 30–90 days at baseline, followed by 30-day monitoring periods during subsequent visits at months 3, 6 and 9. Three digital mobility outcomes were derived: SV95C, representing the fastest 5% of strides; WD95C, representing the longest 5% of walking episodes; and the average number of strides per recording hour.

Statistical Analysis

Analytical Validation of the Refined Algorithm

Analytical validation was conducted using the same methods as those employed in the multiple sclerosis study, ensuring consistency in the validation framework and application of the same predefined criteria (Goldsack et al., 2020). SV95C relies on the ability of the wDHT to correctly detect strides correctly and accurately estimate stride velocity in this population and in conditions representative of daily living. WD95C relies on the ability of the wDHT to detect strides correctly and accurately measure stride length.

Longitudinal study in Daily Living Conditions

Statistical analyses were conducted using Python (version 3.11). Descriptive statistics were applied to summarise population characteristics. Continuous clinical variables were compared between the baseline cohort and the groups assessed at months 3, 6, and 9, using the Wilcoxon rank-sum test. Categorical variables were compared across the same timepoints using the chi-square test of independence. We also conducted group comparisons between the Harvard and Liège cohorts using the same methods.

Compliance was assessed at baseline and longitudinally using the ORD and MRD thresholds previously established in DMD and MS populations.

Reliability was evaluated through the ICC across two consecutive 15-day intervals during the first month of recording. ICC values were interpreted as: <0.50 (poor), 0.50–0.79 (moderate), 0.80–0.89 (good), and >0.90 (excellent).

Clinical validity was assessed through correlations with clinical anchors at baseline, applying Spearman's rank correlation coefficient. Correlation strength was classified as: <0.20 (very weak), 0.20–0.40 (weak), 0.40–0.60 (moderate), 0.60–0.80 (strong), and >0.80 (very strong).

For known-group validity, digital outcome measures were compared across subgroups with different disability profiles at baseline. Patients were stratified by gait impairment (based on ALSFRS-R) and by disease onset type (bulbar, upper-limb, or lower-limb). Group differences were analysed using the Wilcoxon rank-sum test, a non-parametric alternative to the t-test.

Longitudinal data will be assessed with Wilcoxon signed-rank test. SRM was calculated by dividing the mean change in a core by the SD of that change.

IV. RESULTS

Population

A total of 10 and 46 participants were enrolled in the controlled environment and longitudinal study, respectively. In this analysis of the longitudinal study, we include baseline data from the 46 enrolled participants, as well as follow-up data from those who had completed the Month 3 (n = 41), Month 6 (n = 33), and Month 9 (n = 22) visits. Population characteristics are summarised in Table 12

. The patient flow and corresponding data availability at the time of analysis are presented in Figure 20. At baseline, the Liège and Harvard cohorts showed no significant differences in age ($p = 0.76$), gender distribution ($p = 0.48$), disease duration ($p = 0.44$), ALSFRS-R total score ($p = 0.85$), or ambulatory impairment as measured by ALSFRS-R item 8 ($p = 0.84$), indicating comparable populations. Likewise, comparisons between baseline and follow-up groups at 3, 6, and 9 months revealed no significant differences in age ($p = 0.86, 0.51$, and 0.39 , respectively), sex distribution ($p = 0.96, 0.99$, and 0.80 , respectively), disease duration ($p = 0.94, 0.56$, and 0.60 , respectively), ALSFRS-R total score ($p = 0.61, 0.33$, and 0.23 , respectively), or ALSFRS-R item 8 ($p = 0.99, 0.82$, and 0.67 , respectively), confirming that the characteristics of the participants remained consistent over time.

	Analytical Validation Study		Longitudinal Daily Living Study	
Baseline Characteristics	N	Median [min; max]	N	Median [min; max]
Gender	10	7 (70% Male)	46	23 (50% Male)
Age (years): median (IQR) [range]	10	70.5 (65–77) [54–80]	46	60 (55–65.5) [26–79]
Time since symptom onset (years): median (IQR) [range]	10	2.0 (1.1–3.0) [0–3]	46	2.1 (1.6–3.0) [0.8–10.8]
ALSFRS-R (total score)	NA	NA	45	37.7 (5.2) [23–47]
MRC score	NA	NA	44	54.9 (5.3) [38–60]
6MWT	NA	NA	44	371.5 (133.6) [133.2–626.0]
SV95C (m/s)	NA	NA	38	1.0 (0.3) [0.4–1.6]
WD95C	NA	NA	39	64.1 (45.7) [9.1– 253.3]
Nb strides/h	NA	NA	39	147.6 (100.6) [0.1–399.9]

Table 12. Population characteristics of participants with available digital data. *Abbreviations: 6-minute walking test (6MWT), interquartile range (IQR), Medical Research Council score (MRC), not applicable (NA), number of strides per hour (Nb strides/h), Revised ALS Functional Rating Scale (ALSFRS-R), stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C).*

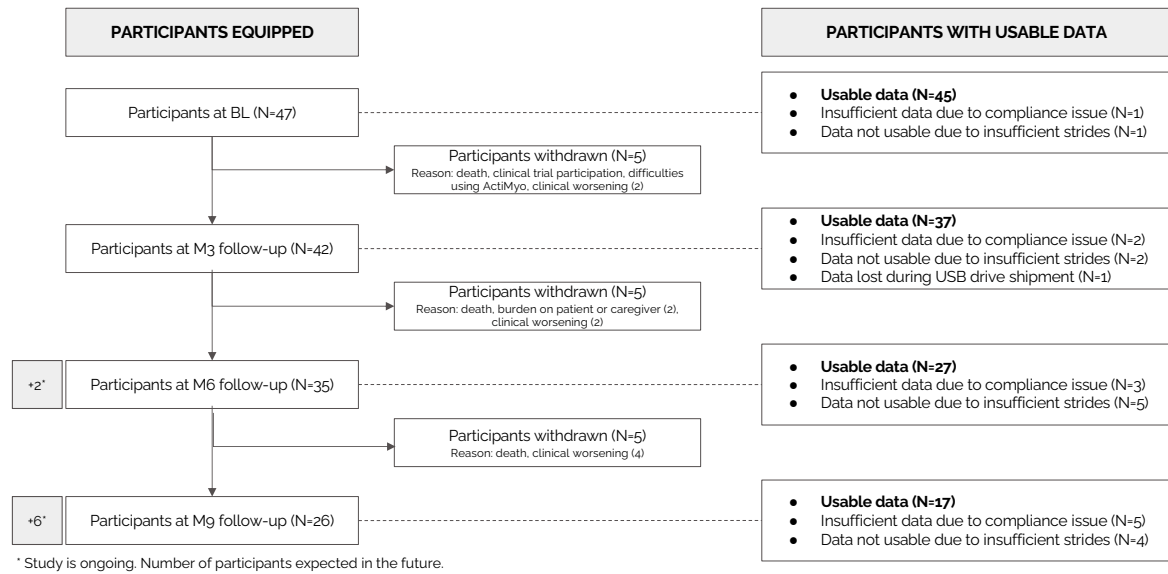


Figure 20. Flow diagram of patient inclusion and data availability. Abbreviations: baseline (BL), month (M).

Analytical Validation

Analytical validation results for stride detection, as well as stride velocity and stride length estimation, are summarised in Table 13. In patients with ALS, the refined algorithm achieved consistently high stride detection performance, with precision exceeding 0.98 and recall exceeding 0.95 across all exercises.

The accuracy of stride velocity and stride length estimates obtained from the wDHT is shown in Figure 21. Both parameters were estimated with low error, with a mean absolute error of 0.02 m/s for stride velocity and 0.03 m for stride length. Variability in the absolute error was also low (SD: 0.02 m/s and 0.03 m, respectively), indicating high precision. These results were stable across both ankles and all exercise conditions (Table 13).

Relative errors remained small across the full measurement range, with mean relative absolute errors between 2.1% and 2.7% for both gait parameters. Agreement between wDHT and motion capture was uniformly strong across exercises, with intraclass correlation coefficients of 0.99–1.00 for stride velocity and 0.99 for stride length, reflecting near-perfect agreement (Table 13).

As shown by Bland–Altman analysis (Figure 21), the ± 1.96 SD limits indicate that 95% of strides were quantified with errors below 9 cm for stride length and 7 cm/s for stride velocity.

		All exercises	Fast walk	Comfortable walk	Dual-Task walk
	TP (number of strides)	5543	1454	2261	1828
	FP (number of strides)	36	4	12	20
	FN (number of strides)	123	5	26	92
	Precision	0.99	1.00	0.99	0.99
	Recall	0.98	1.00	0.99	0.95
Stride velocity	Count	2962	753	1223	986
estimation	Mean absolute error (m/s)	0.02	0.03	0.02	0.02
	Mean relative error (%)	4.27	2.74	5.88	3.45
	SD absolute error (m/s)	0.02	0.03	0.02	0.02
	ICC(1,1) agreement	1.00	1.00	1.00	0.99
Stride length	Count	2962	753	1223	986
estimation	Mean absolute error (m)	0.03	0.03	0.03	0.03
	Mean relative error (%)	4.27	2.74	5.88	3.45
	SD absolute error (m)	0.03	0.03	0.03	0.03
	ICC(1,1) agreement	0.99	0.99	0.99	0.99

Table 13. Metrics for stride detection, stride velocity and length estimation per exercise. *Abbreviations: false negative (FN), false positive (FP), intraclass correlation coefficient (ICC), motion capture (Mocap), standard deviation (SD), true positive (TP), wearable digital health technology (wDHT).*

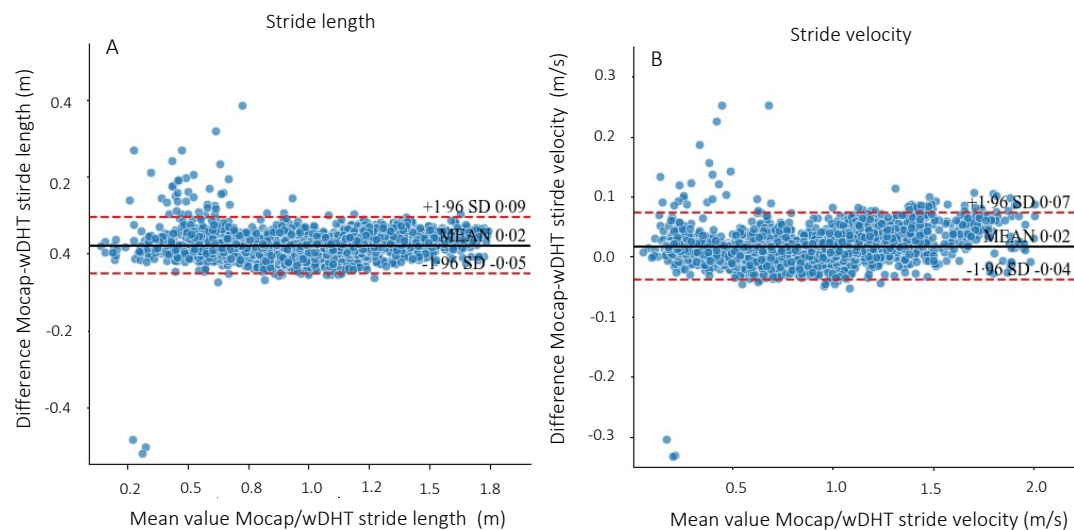


Figure 21. Bland-Altman plots for the error of the stride velocity and length. *Abbreviations: motion capture (Mocap), standard deviation (SD), wearable digital health technology (wDHT).*

wDHT Wear Time and Data Availability

Overall, adherence was good to excellent, with more than 90% of participants providing at least 50 hours per month of wear time through the first 6 months, followed by a decline to 81% at Month 9. Data availability for SV95C was comparatively lower, reflecting the algorithm's requirement for a minimal number of steps.

After refinement, the algorithm showed markedly enhanced sensitivity to stride detection, capturing gait signals even in participants with advanced disease, thereby increasing the number of real-life recording periods available for analysis.

Reliability

Both SV95C and number of strides per hour demonstrated outstanding test–retest reliability, with an ICC of 0.99 and 0.96, respectively, while the reliability of WD95C was good (ICC 0.87), as shown in Table 14.

Digital variables	ICC	
	N*	Period
SV95C (m/s)	38	0.99
WD95C (m)	38	0.87
strides/h	47	0.96

Table 14. ICCs for test–retest reliability of each digital outcome during the first month of recording. *Abbreviations:* number of strides per hour (Nb strides/h), stride velocity 95th centile (SV95C), walking-distance 95th centile (WD95C).

External Validity

As shown in Table 15, correlations between digital mobility outcomes and clinical measures varied in strength across domains. SV95C showed poor correlation with the total ALSFRS-R score ($R = 0.26$, ns), reflecting the multidimensional nature of the scale, which includes several items unrelated to ambulation. In contrast, SV95C demonstrated a strong to very strong correlation with ALSFRS-R GMS ($R = 0.67$, $p < 0.001$), 6MWT ($R = 0.89$, $p < 0.001$) and muscle strength as measured by the MRC score ($R = 0.64$, $p < 0.001$).

Similar patterns were observed for the other digital mobility outcomes. WD95C showed very weak correlation with the total ALSFRS-R score ($R = 0.12$, ns), but moderate correlations with the ALSFRS-R GMS ($R = 0.57$, $p < 0.001$), MRC score ($R = 0.50$, $p < 0.01$). Its correlation with the 6MWT was weaker ($R = 0.53$, $p < 0.001$) compared with SV95C, consistent with its different construct focus.

The number of strides per hour also showed very weak correlation with the total ALSFRS-R score ($R = 0.17$, ns), but moderate correlations with the ALSFRS-R gross motor subscore (GMS) ($R = 0.59$, $p < 0.001$) and MRC score ($R = 0.51$, $p < 0.01$). Its correlation with the 6MWT was strong ($R = 0.69$, $p < 0.001$).

All three digital measures successfully distinguished patients based on their ambulation status as determined by ALSFRS-R question 8 (walking ability) during the baseline recording period. They were also able to differentiate between patients with lower-limb onset and those with upper-limb or bulbar onset as shown in Figure 22.

	ALSFRS-R total	ALSFRS-R GMS	MRC	6MWT
SV95C	0.26	0.67***	0.64***	0.89***
WD95C	0.12	0.57***	0.50**	0.53***
Nb strides/h	0.17	0.59***	0.51**	0.69***

Table 15. Correlations between digital and clinical variables at baseline ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$).

Abbreviations: 6-minute walking test (6MWT), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale gross motor subscore (ALSFRS-R GMS), Medical Research Council scale (MRC), number of strides per hour (Nb strides/h), stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C).

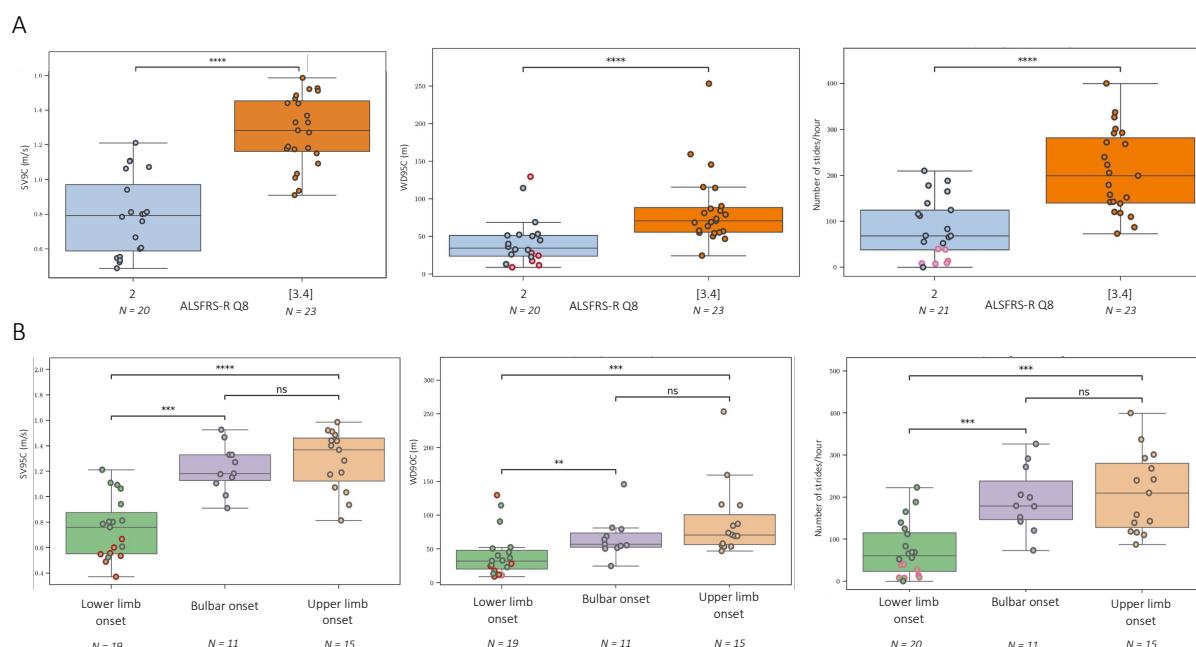


Figure 22. Digital outcome measures by ALSFRS-R walking score (A) and disease onset type (B) ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$, $p < 0.0001^{****}$, ns= not significant). *ALSFRS-R Question 8 - Walking assessment: 4= normal, 3 = early ambulation difficulties, 2 = walks with assistance, 1 = non ambulatory functional movement, 0= no purposeful leg movement.* Abbreviations: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), ALSFRS-R question 8 (Q8), stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C).

Sensitivity to Change

SV95C showed a statistically significant decline at 3, 6, and 9 months ($p = 0.006$, $p = 0.0001$, and $p = 0.002$, respectively) similar to ALSFRS-R ($p = 0.01$, $p = 0.0007$, and $p = 0.002$, respectively) whereas 6MWT only showed significant decline at 6 and 9 months ($p = 0.008$ and $p = 0.02$, respectively), as shown in Figure 23. Number of strides per hour also exhibited significant declines at all time points in the overall population ($p = 0.001$, $p = 0.008$, and $p = 0.0001$, respectively), indicating sensitivity to early and sustained changes in daily ambulation. In contrast,

WD95C did not show statistically significant changes at most time points, suggesting lower sensitivity to change. Individual trajectories are shown in Figure 24.

The absolute SRMs were comparable for SV95C and ALSFRS-R, but higher than the ALSFRS-R GMS and 6MWT at both months 3, 6 and 9 months. Number of strides per hour demonstrated SRMs of similar magnitude to SV95C. In contrast, WD95C showed lower SRMs across all time points. In patients with gait Impairment (defined as ALSFRS-R item 8 < 4), the absolute SRMs were higher for SV95C and number of strides per hour than for ALSFRS-R total, GMS, and 6MWT, as shown in Table 16. WD95C demonstrated modest sensitivity to change in this subgroup, with a significant SRM only at 6 months.

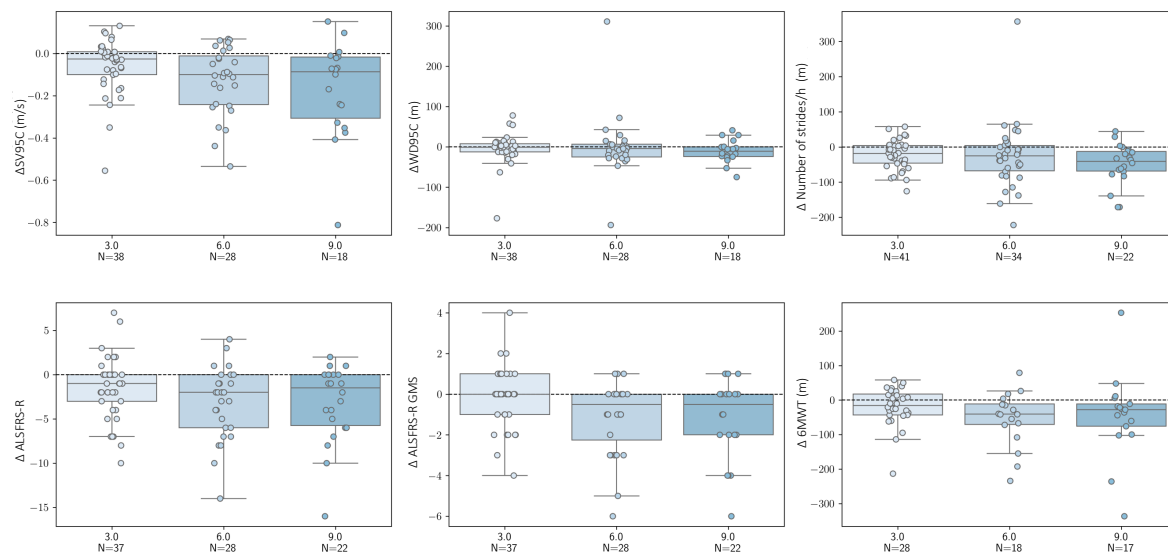


Figure 23. Box plots with change from baseline at 3,6, and 9 months for each digital and clinical outcome ($p < 0.05^*$, $p < 0.01^{**}$). Abbreviations: 6-minute walking test (6MWT), change from baseline (Δ), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale gross motor subscore (ALSFRS-R GMS), stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C).

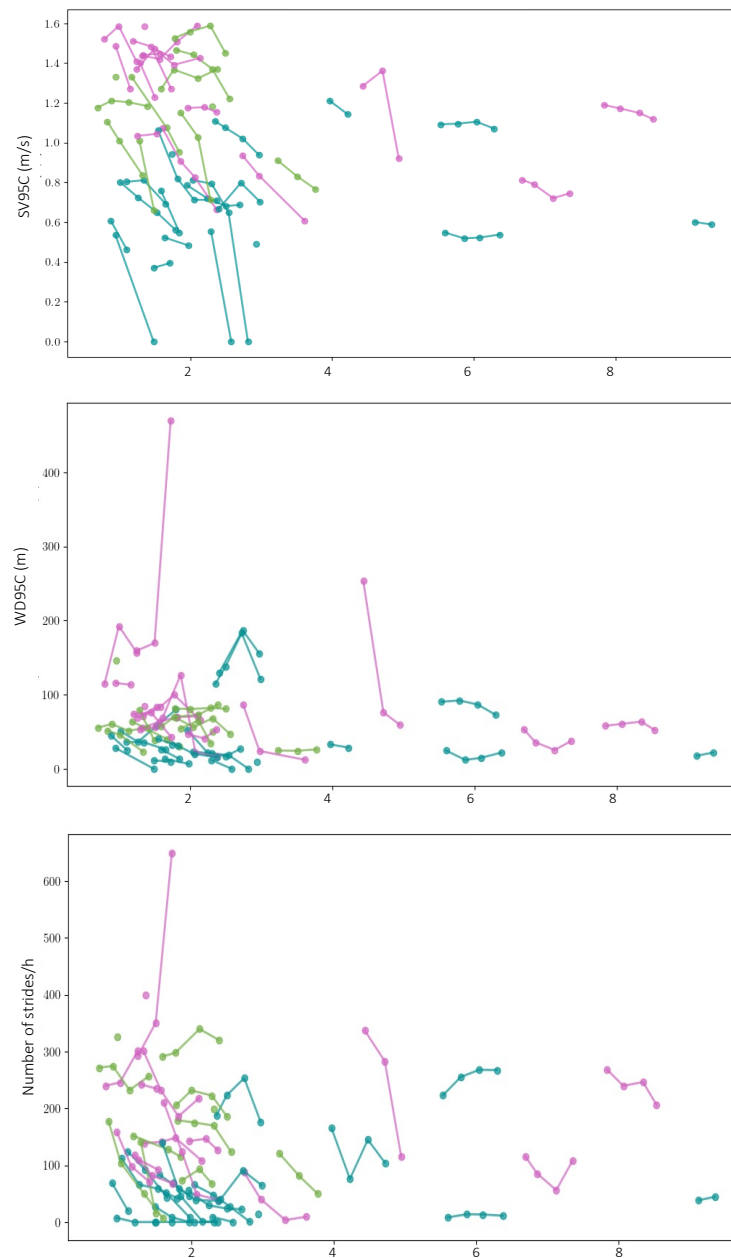


Figure 24. Longitudinal trajectories of individual digital outcome measures over time since symptom onset, stratified by site of symptom onset. Colour-coded by site of symptom onset: lower limb (blue), upper limb (pink), and bulbar (green). Abbreviations: stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C).

Month	Group	3	6	9
ALSFRS-R total score	All population	-0.44* (N=37)	-0.78** (N=28)	-0.75* (N=22)
	Patients with gait impairment at baseline ⁺⁺	-0.24 (N=26)	-0.59* (N=19)	-0.62* (N=14)
ALSFRS-R GMS score	All population	-0.09 (N=37)	-0.64** (N=28)	-0.6* (N=22)
	Patients with gait impairment at baseline ⁺⁺	-0.21 (N=26)	-0.47 (N=19)	-0.4 (N=14)
6MWT	All population	-0.35 (N=28)	-0.69** (N=18)	-0.39* (N=17)
	Patients with gait impairment at baseline ⁺⁺	-0.62* (N=19)	-1.09*** (N=12)	-0.37 (N=10)
SV95C (m/s)	All population	-0.47** (N=38)	-0.81*** (N=28)	-0.8** (N=18)
	Patients with gait impairment at baseline ⁺⁺	-0.66*** (N=26)	-1.00*** (N=17)	-0.93*** (N=11)
Nb strides/h	All population	-0.56** (N=38)	-0.29** (N=28)	-0.89*** (N=18)
	Patients with gait impairment at baseline ⁺⁺	-0.64** (N=26)	-0.65** (N=17)	-0.88** (N=11)
WD95C (m)	All population	-0.11 (N=38)	0.005 (N=28)	-0.37 (N=18)
	Patients with gait impairment at baseline ⁺⁺	-0.19 (N=26)	-0.41* (N=17)	-0.36 (N=11)

Table 16. Sensitivity to change (standardised response mean) of digital and clinical outcomes at 3, 6, and 9 months ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$). ⁺⁺Defined by ALSFRS-R Walking Item < 4. Abbreviations: 6-minute walking test (6MWT), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), Revised Amyotrophic Lateral Sclerosis Functional Rating Scale gross motor subscore (ALSFRS-R GMS), stride velocity 95th centile (SV95C), walking distance 95th centile (WD95C), number of strides per hour (stride/hour).

V. DISCUSSION

This study demonstrated that continuous, passive mobility monitoring using wDHT in patients with ALS is highly feasible, well accepted, and capable of detecting clinically meaningful deterioration in real-world gait.

Feasibility of long-term, unsupervised gait monitoring in this population was supported by high adherence rates over the first 6 months, together with sustained data availability across disease stage.

An important aspect of the analytical validation was the refinement of the stride-detection algorithm to address ALS-specific gait characteristics. This improvement is especially relevant for longitudinal studies in ALS, where progressive weakness can otherwise lead to artificial data loss or bias due to the exclusion of patients with more advanced gait impairment. By enhancing sensitivity to weak and irregular strides, the refined approach supports continued data collection over follow-up and across disease stages. Importantly, these refinements preserved high analytical accuracy for stride velocity and stride length, as evidenced by near-perfect agreement with motion capture across all walking conditions. These findings indicate that the wDHT-derived gait parameters reliably quantify walking behaviour in patients with ALS, including those with more advanced disease.

Among the evaluated digital outcomes, SV95C showed the strongest overall measurement properties, including excellent intra-patient reliability, as well as robust convergent and known-group validity. SV95C showed a significant decline at all timepoints and demonstrated greater sensitivity to change than the ALSFRS-R in patients with gait impairment. These findings highlight the superior sensitivity of SV95C, compared with traditional clinical assessments, for detecting early lower-limb disease progression. Our findings align with and extend previous work supporting the validity of SV95C in neuromuscular diseases such as DMD (European Medicines Agency, n.d.-c; Gidaro et al., 2022) and now provide evidence for its applicability and performance in ALS.

Existing ALS studies using wDHT have primarily examined physical activity rather than stride-level gait metrics (Johnson et al., 2023; Van Unnik et al., 2025) and this is the first study to analyse continuous, real-world stride-level gait parameters in ALS. In this study, SV95C showed a statistically significant decline as early as 3 months, with continued deterioration at Months 6 and 9. While sensitivity to change was comparable between SV95C and the ALSFRS-R in the overall population, SV95C outperformed traditional clinical measures in detecting early and progressive lower-limb decline among patients with ambulation impairment.

Prior work has evaluated sensitivity to change of physical activity metrics over six-month period (Johnson et al., 2023). In the present study, stride count per hour showed comparable sensitivity to change in the overall cohort. However, this metric demonstrated slightly lower measurement reliability and may be more susceptible to external influences, including daily activity patterns, environmental context, and behavioural adaptation, thereby limiting its specificity as a marker of disease progression.

This study has several limitations. First, although adherence to passive monitoring was high, data completeness declined over the course of the study due to participant withdrawal and reduced compliance. However, no significant differences in demographic or disease characteristics were observed among participants across visits, suggesting minimal selection bias. Furthermore, this pattern is expected in ALS studies, in which substantial dropout is common due to rapid progression (van Eijk et al., 2025). Withdrawal rates in this cohort were lower than those reported in similar observational cohorts (Rutkove et al., 2020). Second, data collection is ongoing and several key analyses will require completion of the full first dataset. These include determination of the optimal recording duration (i.e., the minimum monitoring period needed to achieve stable and reliable metrics) and centile-based analyses of stride velocity and walking distance to identify which percentile best captures clinically

meaningful change and is most suitable for assessing patients with ALS. Once we have acquired sufficient longitudinal data, formal assessment of long-term sensitivity to change and predictive validity will also become possible. Third, the present analyses focused exclusively on lower-limb mobility, whereas ALS also affects upper-limb and bulbar function, which will require complementary approaches. The development of ALS-specific digital metrics, including those targeting these functional domains, will therefore be necessary. Finally, the current sample size and phenotype distribution limited the exploration of subgroup-specific effects, such as differences in disease progression patterns. Such analyses may become feasible once the full dataset is available.

Future work should incorporate upper-limb digital metrics based on recent methodological developments (Strackiewicz, Burke, et al., 2024; Strackiewicz, Karas, et al., 2024). The complete longitudinal dataset should be used for trajectory modelling and for assessing predictive performance. Although digital mobility metrics are likely associated with clinically meaningful milestones and survival, these relationships require rigorous validation through extended longitudinal analyses.

To avoid further fragmentation in the field, future efforts should prioritise harmonisation of protocols, moving towards a core set of validated digital outcomes for ALS clinical trials (Van Unnik et al., 2025). Achieving this will require coordinated collaboration among patients, caregivers, clinicians, researchers, and industry partners, particularly as digital outcomes advance towards regulatory qualification.

Taken together, these findings support integration of digital mobility outcomes into ALS clinical research. Continuous real-world gait monitoring offers an ecologically valid, highly sensitive characterisation of ambulation decline, while reducing dependence on burdensome in-clinic assessments. Addressing remaining challenges, including improved data collection in advanced disease, validation in larger and more diverse cohorts, and advancement along regulatory pathways, will be essential to realise the translational potential of wDHT-based gait measures into therapeutic endpoints.

VI. KEY INSIGHTS

Preliminary data support the feasibility of using ankle-worn sensors to assess real-world ambulation in ALS.

Wearable-derived digital outcomes, particularly SV95C, are reliable, and clinically meaningful measures of ambulation in ALS. Longitudinal data are being acquired to assess sensitivity to disease progression and predictability of digital outcome derived from wDHT. Further work should also focus on upper limb assessment.

Preliminary findings support the feasibility and acceptability of continuous, passive real-world ambulation monitoring in ALS. Wearable-derived digital mobility outcomes, particularly the SV95C, demonstrated strong measurement properties, including high reliability and clinical relevance, and sensitivity to disease progression, especially among patients with gait impairment.

Future work should expand digital assessment beyond lower-limb mobility to include upper-limb function, supporting a more comprehensive characterisation of ALS progression.

PARKINSON'S DISEASE

The following chapter presents the results published in the article entitled “Wearable inertial device for monitoring Parkinson’s disease symptoms: a pilot study in a controlled environment” by M. Poleur et al., published in Scientific Report. This article is not reproduced in its entirety.

I. CLINICAL OVERVIEW

PD is a chronic neurodegenerative disease primarily affecting dopaminergic neurons of the Substantia nigra pars compacta. It is the second most common neurodegenerative disease after Alzheimer’s disease (Erkinen et al., 2018). PD is defined by the presence of parkinsonism – characterised by bradykinesia combined with either resting tremor or rigidity – in combination with supportive criteria and in the absence of exclusion criteria (Postuma et al., 2015). Diagnosis remains challenging, especially at an early stage, as no definitive biomarkers exist (Hughes et al., 1992). A good and sustained response to levodopa (L-dopa) may help support the diagnosis (Postuma et al., 2015).

Current treatments aim to compensate for dopamine loss using L-dopa or dopamine receptor agonists (Armstrong & Okun, 2020). However, none of these drugs prevent neuronal degeneration and disease progression. As the disease progresses, patients ineluctably develop L-dopa-induced motor complications, such as motor fluctuation and dyskinesia partly linked to the iterative administration of L-dopa and its pulsatile effects on dopaminergic receptors (Fabbrini & Guerra, 2021; Heumann et al., 2014).

Clinical assessment of PD typically relies on scales such as the MDS-UPDRS (Goetz et al., 2008). However, these assessments have psychometric limitations, including lack of inter-rater reliability (Marras & Lang, 2004), poor sensitivity to subtle changes, particularly in early stages (Regnault et al., 2019), and dependence on hospital-based, episodic evaluations that fail to capture daily fluctuations (Ahlskog & Muenter, 2001).

With recent advances in the therapeutic field, an increasing number of promising trials are emerging for PD (McFarthing et al., 2023). As therapeutic decisions and drug development rely on accurate, objective, and representative evaluations of patient’s condition, the ability to continuously monitor a patient’s activity and symptoms remains a significant challenge.

The emergence of wearable sensor technology offers new opportunities for continuous, objective symptom monitoring (Piwek et al., 2016). Accelerometers, gyroscopes, and their combination, known as IMUs, are the most widely used wearable sensors for assessing symptoms and motor complications in neurological diseases (Yang & Hsu, 2010). They have already been used for various purpose in the neurological field (Sica et al., 2021; Zhao et

al., 2023). Objective measurement of various PD motor manifestations, including gait impairments, bradykinesia, tremors, dyskinesia and motor fluctuations, outside clinical settings using wearable inertial devices has proven feasible, achieving accuracies exceeding 90% (Sica et al., 2021). In recent years, the use of wearable sensors to objectively measure PD motor manifestations has known a growing interest, as highlighted in recent comprehensive reviews (Moreau et al., 2023). Some studies have focused on postural and gait disturbances, while others investigated PD symptoms and their fluctuations aiming to detect bradykinesia, tremor, dyskinesia, and ON/OFF state episodes in real-life conditions (Sica et al., 2021). Only few devices have shown their ability to assess all aspects of the disease (Rodríguez-Martín et al., 2022). ML approaches for identifying PD motor manifestations have shown remarkable potential (Del Din et al., 2021), including in detecting patients with prodromal PD (Schalkamp et al., 2023). While this could be a valuable tool for selecting participants in clinical trials for neuroprotective treatments, it remains uncertain if these models could be generalised outside the studied population, raising concerns about their clinical applicability. Additionally, most existing devices and algorithms have yet to prove their efficiency in real-life conditions (Del Din et al., 2021), likely due to the lack of validated reference outcome for comparison.

II. AIM

The aim of this study was to evaluate whether movement reconstruction using a wearable inertial device can accurately identify key PD motor manifestations, including tremor, akinesia, and dyskinesia, on an individual movement basis.

III. METHODS

Study Design

This pilot multicentric study on patients with PD (Pre-QuantiPark), was sponsored by the Institute of Myology at La Pitié-Salpêtrière University Hospital. The 12-months study was conducted at two French investigational sites of the APHP: La Pitié-Salpêtrière Hospital, Paris, and Henri Mondor Hospital, Créteil.

Standard Protocol Approvals, Registration and Patient Consents

The study protocol was approved by the local ethics committee (CPP-Ile de France VI – Groupe Hospitalier La Pitié-Salpêtrière, ID RCB: 2016-A00121-50; ClinicalTrials.gov Identifier: NCT02785978). All patients gave written informed consent prior to participation in this exploratory study. The study was conducted in accordance with relevant guidelines and regulations, including the Declaration of Helsinki and Good Clinical Practice guidelines.

Participants

Ten patients with PD were enrolled. Participants were recruited among PD patients undergoing pre-surgical evaluation for DBS. The inclusion criteria were subjects aged ≥ 18 years old with a clinical diagnosis of idiopathic PD (Movement Disorder Society criteria); stable parkinsonian medication regimen including L-dopa for at least 4

weeks; experience of motor fluctuations and dyskinesia, and a normal Montreal Cognitive Assessment test (MoCA) ≥ 26 (out of 30). The exclusion criteria were previous surgery for the treatment of PD, patients treated with apomorphine or L-dopa pump, patients treated with DBS, patients with drug-induced parkinsonism, vascular parkinsonism or Parkinson plus syndromes (such as multiple system atrophy (MSA), PSP, and cortico-basal syndrome), as well as pregnant and breast-feeding women.

Data Collection

Demographic and clinical data, along with treatment and medical histories, were collected before the L-dopa acute challenge, which was scheduled during a planned hospitalisation as part of routine care.

Controlled environment tests, including a series of everyday-life tasks, MDS-UPDRS, and Rush Dyskinesia Rating Scale (RDRS) assessments, were performed before the L-dopa challenge test (LCT). All test sessions, including the LCT evaluation periods, were videotaped and simultaneously recorded using a wearable IMU device (Figure 25).

LCT was conducted by physicians and/or nurses experienced in movement disorders. The trial involved a single-dose L-dopa challenge. Prior to the visit, patients discontinued all dopaminergic medications for at least 12 hours (over 18 hours for dopaminergic agonists and 24 hours for long-acting agonists) to induce a practically defined “OFF medication” state. The LCT was performed early in the morning on an empty stomach. A L-dopa equivalent dose (LEDD) (Tomlinson et al., 2010) corresponding to the patient’s first morning dose, increased by 50% or 100 mg, was administered.

Clinical evaluations were conducted before any drug intake (“OFF state”) and then every 15 minutes for 90 minutes following the L-dopa administration. These evaluations included the MDS-UPDRS Part III (motor section).

Controlled environment tests were recorded with the ActiMyo magneto-inertial device (SYSNAV, Vernon, France) as depicted in Figure 25. Simultaneously, video recordings were captured using a tripod-mounted camera. Recording started as soon as the sensors were removed from the docking station and ended at the conclusion of the test. A synchronisation signal was applied at the start of the session to align the video and wearable device data.

Videos were independently and blindly analysed by two neurologists (TG and BD), who assessed each movement detected by the wearable device and calculated corresponding negative and positive predictive values. Their assessments were then compared, and any discrepancies were resolved through qualitative consensus. Drug-related dyskinesia (such as OFF-period dystonia, diphasic or peak-dose dyskinesia) has been evaluated by an expert in movement disorder (BD) and reported on the dedicated worksheet. Adverse events have been monitored.

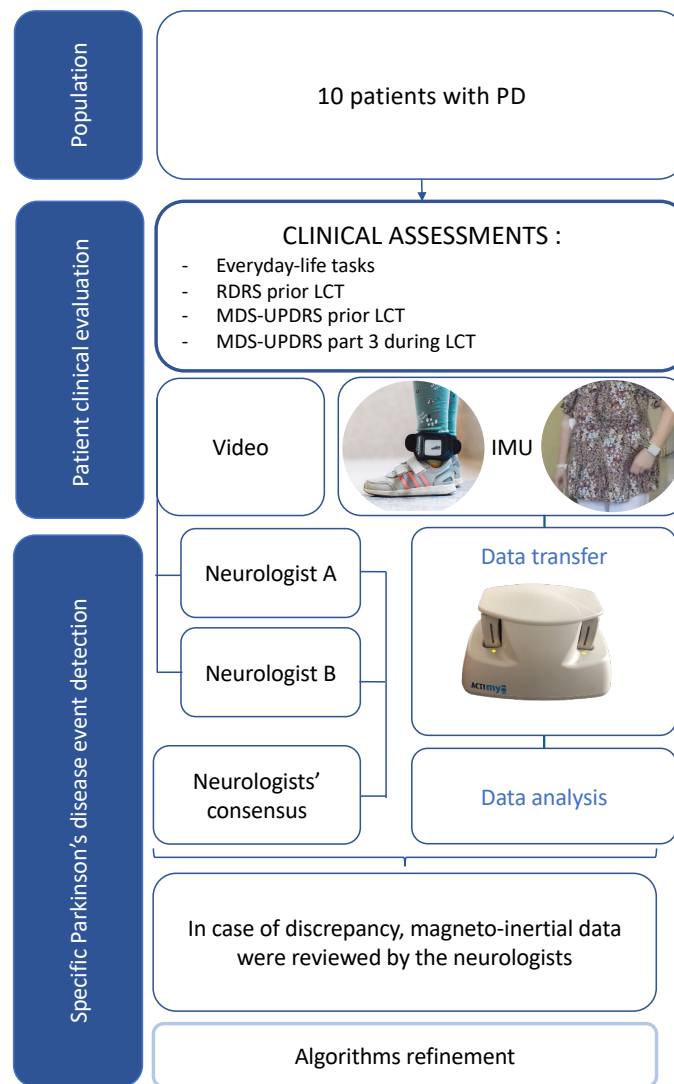


Figure 25. Flow chart and method for specific PD events detection. Abbreviations: inertial measurement unit (IMU), L-dopa challenge test (LCT), Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), Parkinson’s disease (PD), Rush Dyskinesia Rating Scale (RDRS).

Data proceeding and extracted parameters

Algorithms for PD manifestations detection

The device includes two sensors attached to the wrist and ankle of the side most affected by PD. Each sensor contains high precision triaxial accelerometers, gyroscopes, magnetometers, a temperature sensor, and a barometer. These sensors recorded passively upper and lower limbs linear acceleration and angular velocity in 3-dimensions. Data are recorded at a sampling frequency of 130.69 Hz. The sensors are encased in a lightweight plastic housing (43 × 37 × 16 mm; 28 g) and are individually factory-calibrated to ensure accuracy across a range of temperature, pressure, and dynamic conditions. These measurements have been used to develop an automatic detection of parkinsonian manifestations. These manifestations are tremors, akinesia and dyskinesia. The data were analysed using MATLAB and Python.

Tremors are characterised by repeated, regular and oscillatory movements at the frequencies between 4 and 7Hz. The frequency spectrum is computed using a fast Fourier transform on a sliding window of 8 seconds. To demonstrate the presence of a tremor, a peak should be detected between 4 and 7Hz in one of the axes of the accelerometer and in one of the axes of the gyroscope. In addition, this peak must be of large magnitude (at least twice as large) compared to the signal measured between 0.8 and 2.5Hz.

Akinesia is detected when the sensor could only detect very few movements. The absence of movement is identified by computing the SD of the norm of the gyroscope and the accelerometer on a sliding 5-minutes window. If both SD are between 0.2 and 4 degrees per second in the window, we assumed that the patient presented akinesia during this time window.

Dyskinesia was detected in the ankle and defined as prolonged, high-amplitude movement which is not associated with walking or tremor. The frequency spectrums of the norm of the accelerometer and the gyroscope were calculated on 8 seconds sliding window. A candidate dyskinesia is considered in the window if we observe a peak in the lower frequency band (0.8-2.5Hz). Windows containing tremor activity or physiologically normal leg movements were discarded, and the remaining events were classified as dyskinesia. The movement intensity threshold was set to exclude most voluntary actions, thereby improving the discrimination between involuntary dyskinetic and intentional movements.

Algorithms for event detection are based on prior validated signal processing approaches developed for motion reconstruction in neuromuscular disorders. These algorithms were initially developed and tested on a prior unpublished cohort of PD patients and were refined and optimised during the present study, as planned in the study protocol.

As illustrated in Figure 25, algorithms for event detection and analysis have been compared to the simultaneous and independent evaluation of the set of videos, by two neurologists (TG and BD).

Statistical analysis

The accuracy of the proposed algorithms was tested by using the confusion matrix comparing data from the algorithms and the observations of neurologists. This confusion matrix includes the following details: true positive (TP) for correctly predicted event values; false negative (FN) for incorrectly predicted no-event values; true negative (TN) for correctly predicted no-event values and false positive (FP): for incorrectly predicted event values. Metrics for performance were computed for the duration of time spent on each symptom. Sensitivity, specificity, precision and accuracy are expressed, as described below, in terms of TP, TN, FN and FP.

- Precision (or positive predictive value) = $TP / (TP + FP)$ = (Number of correct positive assessments)/(Number of positive assessments)
- Sensitivity = $TP / (TP + FN)$ = (Number of true positive assessment)/(Number of all positive assessment)
- Specificity = $TN / (TN + FP)$ = (Number of true negative assessment)/(Number of all negative assessment)
- Accuracy = $(TN + TP) / (TN + TP + FN + FP)$ = (Number of correct assessments)/Number of all assessments

We used Wilcoxon rank-sum test to compare differences between PD motor manifestations detected by sensors before and after LCT.

IV. RESULTS

Study Population

Baseline demographic and clinical characteristics of the study population are presented in Table 17. A total of 10 PD patients were included. All patients were treated with L-dopa with a median LEDD of 1139.3 mg/day. All patients reported dyskinesia at inclusion. Among them 90% reported peak dose dyskinesia. No participants reported any adverse event related to the study.

Sensor Algorithm Performance

During the LCT, the algorithm of PD motor manifestations detection by the sensor showed an overall good result. The sensor detects an improvement of PD motor manifestations during the L-dopa test as shown by the reduction of tremor and akinesia after L-dopa administration. Precision, sensitivity, specificity and accuracy are shown in Table 18. The performance of the algorithm for the detection of PD motor manifestations is illustrated in Figure 26B.

DEMOGRAPHIC CHARACTERISTICS	
Sample size	10
Gender: number of female (%)	4 (40)
Age at inclusion (years)	55.2 ± 9.8 [40–69]
Disease Duration (years)	10.7 ± 3.6 [6–16]
TREATMENT	
Number of intake/days	5.2 ± 1.4 [2–7]
L-dopa equivalent dose* (mg)	1302.3 ± 295.0 [850–1722.5]
CLINICAL CHARACTERISTICS	
MDS-UPDRS	
Total score (/260)	60 ± 15.9 [42–90]
Part 1 (/52)	12.3 ± 4.8 [7–21]
Part 2 (/52)	14.5 ± 3.9 [10–24]
Part 3 (/132)	23.8 ± 11.7 [7–43]
Part 4 (/24)	9.4 ± 3.4 [2–14]
RDRS score	
Total score	1.3 ± 1.1 [0–3]

Table 17. Demographic and clinical characteristics of participants. Data are expressed in mean ± SD [Min–Max].

*Calculated as previously described (Tomlinson et al., 2010). Abbreviations: L-dopa equivalent dose (LEDD), Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), Revised Dyskinesia Rating Scale (RDRS), standard deviation (SD).

	Dyskinesia	Wrist tremor	Ankle tremor	Wrist akinesia	Ankle akinesia
True positive (%)	2.9	19.0	11.0	3.2	17.0
True negative (%)	93.0	78.0	83.0	97	78.0
False positive (%)	1.5	3.0	5.8	0.0	4.8
False negative (%)	2.2	0.0	0.0	0.0	0.0
Precision (%)	65.9	86.4	65.5	100.0	77.9
Sensitivity (%)	56.9	100.0	100.0	100.0	100.0
Specificity (%)	98.4	96.3	93.5	100.0	94.2
Accuracy (%)	96.3	97.0	94.2	100.0	95.2

Table 18. Precision, Sensitivity, Specificity, Accuracy for detection of each PD symptom.

L-Dopa Challenge Test Results

L-dopa test was positive in all 10 patients with PD. Mean MDS-UPDRS motor scores were 48.7 ± 11.5 in OFF state and 37.7 ± 14.1, 25.7 ± 5.5, 18.6 ± 5.0 and 18.4 ± 5.5 at 15, 30, 60 and 90 minutes after acute L-dopa intake, respectively. After 90 minutes, a 62.1 ± 18.7% (– 30 points) mean reduction in MDS-UPDRS motor score has been achieved. The evolution of PD motor manifestations detected by sensors using 15-minute windows is shown for

each patient in Figure 26A. Based on the Wilcoxon rank-sum test results, we observed a significant difference between the proportion of time with dyskinesia ($p=0.0169$) and tremor recorded at the wrist ($p=0.0247$) before (15min before) and after (between 45 and 60min after) L-dopa intake, but no significant difference for the tremor recorded at the ankle ($p=0.5415$) and akinesia recorded at wrist and ankle ($p=0.3173$ and $p=0.0798$, respectively).

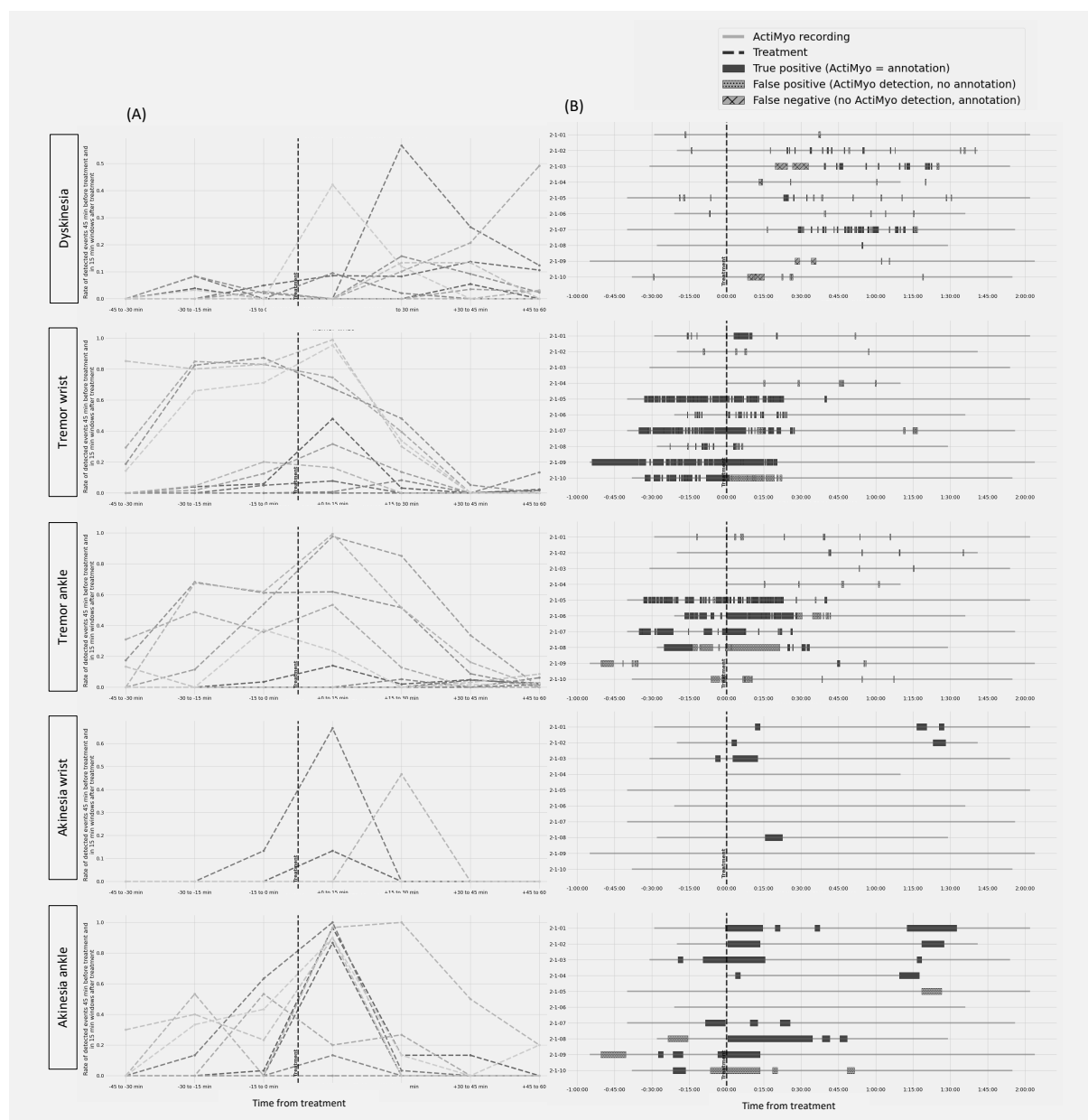


Figure 26. Sensor detection during LCT for each PD motor manifestation for all patients per 15-minute windows (A). Sensor performance during LCT for each PD motor manifestation for all patients (B). *In green, sensor detection of events and in orange the false negatives. The intake of L-dopa is marked with a dotted black line.*

V. DISCUSSION

Our pilot study suggested that a magneto-inertial wearable sensor could accurately detect akinesia, tremor and dyskinesia; the main parkinsonian symptoms observed in PD patients. Recent technological advances have made

continuous monitoring of neurological manifestations possible, with growing interest in wearable devices for real-life data collection (Lu et al., 2020b). The COVID-19 pandemic has further highlighted the need for reliable, validated tools to assess patients remotely, both in clinical trials and routine practice.

Previous studies have suggested that remote monitoring can help identify patients who may be candidates for advanced therapies (Kadirvelu et al., 2023a) or improved management of PD (Woodrow et al., 2020). However, these data were often based on global indices derived from spectral analysis of movement. Our results demonstrate that individual movements associated with PD can be accurately identified in a controlled environment using a magneto-inertial device. The lower agreement with physicians observed for dyskinesia reflects the challenge of distinguishing these movements from normal ones with similar trajectories.

Importantly, our algorithms were validated against a set of synchronised videos independently and blindly analysed by two neurologists, providing for each symptom negative and positive predictive values. While video-based validation has been applied for freezing of gait (Capecci et al., 2016) and balance assessment (Stack et al., 2018), it has not yet been applied to the detection of individual PD movements. This constitutes the key novelty of our study and provides a crucial methodological foundation for future large-scale validation efforts.

These preliminary findings provide a strong rationale for further investigations in a larger and more diverse population, particularly in unsupervised settings where symptom monitoring can more reflect real-life conditions. To assess the clinical relevance of wearable-based symptom detection, future studies should establish a robust reference for symptom occurrence, as traditional symptom diaries remain unreliable due to subjective reporting and recall bias (Papapetropoulos, 2011). A key challenge will be identifying an objective and accurate “ground truth” for symptoms, possibly through a combination of clinician assessments and real-time patient feedback. Expanding data collection to a longitudinal, real-world framework will also allow better tracking of symptom fluctuations, disease progression, and treatment responses over time, refining algorithms and improving their accuracy.

Our algorithms were designed using a standard methodology based on movement disorder and PD knowledge rather than ML. While simple algorithms effectively detect clear manifestations such as tremor, they are less reliable for complex movements like dyskinesia. Distinguishing akinesia from inactivity in real life is also expected to be challenging. A ML approach could improve accuracy but would require extensive data collection (Schalkamp et al., 2023). The main drawback of such an approach is the lack of interpretability for clinicians.

Despite these promising results, certain limitations exist at this stage. This study was primarily designed as a proof of concept in a controlled setting, and participants were DBS candidates with a complex Parkinson’s disease phenotype, including L-dopa-induced motor complications. As such, the study population represents a highly specific subgroup of patients, which may limit the generalisability of the findings to the broader Parkinson’s disease population. This selection bias may also have complicated the distinction between different motor events. In addition, clinical phenotype data (e.g., tremor-dominant versus akinetic-rigid subtypes) were not collected. As clinical phenotypes may influence the expression, distribution, and progression of motor manifestations, their

absence may limit the interpretation of the findings (Rigon et al., 2026). In addition, the small sample size further limits the generalisability of our findings. Moreover, as the algorithms were initially developed and tested on a prior unpublished cohort of PD patients and subsequently refined during the present study, there is a potential risk of an overestimation of algorithm accuracy. Furthermore, the current algorithm for dyskinesia detection excludes episodes that occur simultaneously with walking or tremor. In addition, dyskinesia detection was based solely on signals from the ankle sensor, as reliable detection from upper-limb sensors was not feasible due to the difficulty in distinguishing involuntary movements from physiological voluntary activity. This represents an important limitation, as dyskinesia also commonly involves the upper limbs, trunk, and head. (Goetz et al., 2008). We acknowledge that this may lead to underestimation of dyskinesia, particularly in upper limb and during walking, and that further engineering work will be required to address this limitation.

Consequently, the results should be interpreted with caution and viewed as exploratory and hypothesis-generating, warranting validation in larger and more diverse cohorts to ensure external validity and reproducibility. The next step will also be to assess PD motor manifestations in real-life conditions, the ultimate goal of continuous digital assessment. Future studies should refine algorithms for detecting dyskinesia and akinesia. Since the device used here has already been well-validated for gait impairment detection in DMD (European Medicines Agency, n.d.-c; Servais et al., 2023) including comparison with controls and is currently being validated in other neurological disorders (Gidaro et al., 2022; Poleur et al., 2024, 2026), future research should aim to integrate gait and PD symptom assessment in real-life environments.

Beyond methodological considerations, regulatory qualification remains a critical challenge. Only a limited number of wearable devices have obtained FDA clearance in PD, while some others hold CE marking. However, the variables they generate remain largely unqualified by regulatory bodies such as the FDA and EMA. Despite the promise of wearable devices for remote monitoring, technical issues, poorly validated outcome measures and regulatory limitations remain significant barriers. A few years ago, the Movement Disorder Society Task Force on technology published concrete steps to facilitate adoption of mobile health technologies in clinical practice (Espay et al., 2019b). The recent qualification of a digital outcome, the SV95C, in DMD and its use as a primary endpoint in several pivotal trials open the perspective of further qualification of digital outcome, and PD is certainly an area of considerable unmet need.

Achieving regulatory qualification will require large, prospective, multi-sites real-world studies to establish usability, validity, reliability, clinical meaningfulness and sensitivity to change. Massive data acquisition, algorithm refinement, and psychometric validation of digital outcomes will be necessary. This can only be achieved through strong collaboration between patients, physicians, engineers, regulators, and the pharma industry. This study represents an initial step towards real-life monitoring.

VI. KEY INSIGHTS

We have demonstrated the accuracy of PD symptom detection in a controlled environment. This work represents an initial step towards identifying metrics that can be applied in real-life settings for symptom-specific monitoring. The primary objective of this proof-of-concept study was to increase the granularity of analysis down to the level of individual movements, allowing a more detailed characterisation of motor manifestations. Further validation in a larger cohort will be required to refine the event-detection algorithms, and the feasibility of using this technology outside clinical facilities will need to be demonstrated by real-world data acquisition. Importantly, the significance of this work does not lie in introducing yet another sensor to the Parkinson's disease market, but rather in its methodological contribution. To our knowledge, this study provides the first movement-by-movement validation of a wearable device in Parkinson's disease, thereby establishing a new approach for high-resolution, symptom-specific assessment.

GENERAL DISCUSSION

I. LESSONS LEARNED FROM THIS WORK

Movement monitoring offers a unique opportunity for continuous and objective assessment of neurological diseases, provided that a disease-by-disease validation approach is applied. This work highlights several strengths in the application of wDHTs to neurological diseases. The key advantage is the ability to continuously collect objective, high-resolution data in real-world settings. This approach captures ecologically valid information including fluctuations and subtle changes in motor function that may be overlooked during in-clinic assessments. Consequently, longitudinal monitoring not only enhances sensitivity to disease progression but also holds promise for the early detection of disease signs and progression.

In previous chapters, our results have been discussed separately for each disease, as findings from movement monitoring can only be generalised to a limited extent. Each neurological condition is characterised by distinct pathophysiological mechanisms, different motor impairments, and specific clinical as well as technical challenges that must be carefully considered when designing and interpreting movement monitoring. Consequently, the optimal recording duration and analytical windows should be adapted to the pathophysiology and temporal dynamics of each disease. For example, in DMD, the progressive nature of muscle weakness justifies periodic long-term recordings to monitor functional decline, whereas in ALS, disease progression occurs much more rapidly. In such cases, shorter recording periods are preferable to maintain reliability and limit confounding effects of functional decline, while shorter intervals between recording periods allow for more frequent assessment of change. Furthermore, shorter study durations are also required to preserve feasibility, given the high withdrawal rates observed due to the rapidly progressive nature of the disease (van Eijk et al., 2025). In conditions such as PD, motor performance fluctuates over short timeframes rather than showing a steady decline, making it essential to use shorter observation windows that can accurately capture these dynamic variations.

Beyond temporal considerations, gait and mobility characteristics are differentially influenced by disease-specific neurological symptoms. Distal weakness may affect foot clearance and step length, proximal weakness can result in a waddling gait and difficulty with stair climbing, and features such as ataxia or spasticity further increase gait variability and asymmetry. Together, these patterns complicate data interpretation and make a single, fit-for-purpose solution based on a single outcome measure unworkable.

Given these disease-specific considerations, outcome evaluation must be carefully contextualised. Nevertheless, it is also valuable to adopt a broader perspective and examine findings across different studies and conditions. Indeed, shared insights may emerge that could contribute to a more comprehensive understanding of the

potential and limitations of movement monitoring technologies. Moreover, because validation and regulatory qualification are both time- and resource-consuming, adopting this broader view could help identify common pathways and support the faster development of digital outcomes across multiple indications.

The work presented in this thesis demonstrates the feasibility of implementing wDHTs across diverse patient populations and neurological conditions. Across various conditions, digital outcomes were able to capture relevant clinical features, due to their adaptability to disease-specific constraints, including usability in very weak patients with neuromuscular disorders, the need to capture unpredictable motor fluctuations in Parkinson's disease, and the ability to characterise long-term progression in multiple sclerosis.

Despite differences in age, disability level, and clinical context, patients were generally able to wear the devices and provide interpretable data. Overall compliance was high, although adherence tended to decline during longer follow-up periods. Compliance nevertheless remains a challenge in certain populations, particularly in conditions associated with cognitive impairment, such as ALS or other disorders not addressed in this work (e.g. DM1 or Angelman syndrome), where adherence to monitoring protocols may be reduced. In addition, differences between children, whose parents typically manage sensor placement, and adults, who may experience social or professional constraints, must be considered when planning long-term recordings.

Taken together, these findings confirm that remote monitoring is not only technically achievable but also acceptable to patients with various neurological diseases.

In addition to feasibility, digital outcomes demonstrated excellent known-groups validity, effectively distinguishing patients from controls and differentiating between groups with varying levels of disability across all diseases. Furthermore, we observed moderate-to-strong correlations between traditional in-clinic assessments and the digital outcomes. These correlations confirm that the digital measures capture clinically relevant aspects of the different diseases. Importantly, aiming for perfect correlation would be counterproductive, as digital outcomes are not intended to replicate traditional clinical assessments but rather to complement them.

When comparing different digital outcomes, specific gait parameters such as SV95C usually perform better than cumulative measures of general physical activity, including strides per hour. SV95C has demonstrated greater reliability, sensitivity to change, and clinical validity. Higher reliability is expected for SV95C, whereas cumulative activity measures are strongly influenced by lifestyle, motivation, and environmental context. These findings are consistent with previous observations in DMD (European Medicines Agency, n.d.-c) and FSHD (Gidaro et al., 2022). As a result, specific gait parameters are emerging as more robust biomarkers to evaluate disease progression and therapeutic response.

However, this may not apply to diseases in which severe and rapidly progressive impairment becomes the primary driver of physical activity, overwhelming external influences. In such conditions, including ALS, cumulative activity measures such as step count may more directly reflect disease progression, as declining motor function

increasingly constrains daily activity regardless of behavioural or environmental factors. In this specific context, the performance of step-based metrics appears comparable to that of walking speed metrics, such as SV95C.

Beyond quantitative performance, digital outcomes consistently provided real-life information that complemented traditional clinical assessments, offering insights that remain undetectable by conventional scales. Indeed, in some diseases such as ALS or MS, digital outcomes seem more sensitive to change than traditional measures, as previously demonstrated in DMD (European Medicines Agency, n.d.-c). In MS, SV95C even revealed subtle deterioration in the RRMS population that standard functional scores failed to detect over the same period. In PD, digital monitoring offers a valuable opportunity to quantify motor fluctuations and treatment responses in real-world settings. However, this latter aspect could not be explored in the present work due to time and funding constraints.

Overall, wDHTs go beyond conventional outcome measures by providing more sensitive and granular insights into everyday performance. By moving assessment beyond the artificial context of the clinic, real-world monitoring helps account for day-to-day variability, compensatory strategies, the Hawthorne effect (Jeon et al., 2023) and contextual factors such as fatigue or environment. In addition to its practical utility for evaluating treatment response, real-world monitoring may improve our understanding of patients' functional performance and symptoms in daily life.

Finally, this work highlights the importance of integration between disciplines and between clinical and patient perspectives. The future of digital outcomes lies not only in refining algorithms or improving the precision of the sensors, but also in integrating these outcomes within a broader system of clinical care and research.

Strengths

This work has three main strengths. The first one lies in its systematic approach, which is guided by well-established psychometric principles and frameworks (Goldsack et al., 2021). By grounding these studies in these rigorous standards, we ensured that the evaluation of digital outcomes is both methodologically robust and clinically meaningful. Furthermore, in our studies, we used a device that has already undergone regulatory qualification, demonstrating that these methods can be applied in many fields of neurology.

Another strength of this approach lies in the patient's perspective. Remote monitoring has the potential to reduce the burden of frequent hospital visits. It may also be used in the future to improve patient engagement in their care by providing individuals with insight into their health status at a higher level of precision than simple step count. Importantly, these approaches can extend access to care and research participation for patients living in remote areas or facing transportation difficulties, supporting more inclusive studies and healthcare system.

Finally, the most important strength of this specific work may be the collaboration we have established with multidisciplinary teams, including medical experts from different countries, engineers, and members from the pharmaceutical industry, who significantly enhanced the quality and relevance of our work. In addition, working

with specialists from around the world has been enriching, not only for this project but also on a personal level. The expertise our research team developed in movement analysis became truly meaningful only through the contributions of disease specialists, who brought essential knowledge of pathophysiology, clinical presentation, and unmet needs specific to each condition.

Based on our collective efforts, the device used in this work and the digital outcomes we have contributed to validate are now being used as exploratory endpoints in clinical trials for both MS and ALS. This represents a critical milestone, along the path paved by the EMA qualification in DMD. These developments underscore the direct translational potential of our work, demonstrating that rigorously validated digital measures can progress beyond academic research and be integrated into drug-development programmes.

...and Limitations

Several limitations should be acknowledged. First, the studies presented in this thesis are small-scale academic investigations, contributing to a growing but heterogeneous body of evidence. The strength of the evidence varies across conditions, underscoring the preliminary nature of some findings, particularly in diseases such as PD. In addition, study populations were relatively small, and our findings will need to be confirmed on larger, independent, multicentre cohorts.

Certain aspects of psychometric evaluation were not addressed. Assessing content validity would have required a dedicated approach, such as expert panel evaluations or qualitative interviews with participants, which were not incorporated into the study protocols.

Furthermore, the relatively short follow-up durations in the longitudinal studies limited the ability to fully characterise long-term sensitivity to disease progression. For instance, in MS, although two assessments one year apart were initially planned, shorter intervals and additional time points are required to capture more subtle changes and confirm progression patterns. Similarly, the limited duration of these longitudinal studies prevented adequate evaluation of the predictive value of digital outcomes for clinical anchors, such as loss of ambulation or death in ALS.

The validation of a clinical outcome measure requires long-term commitment, sustained effort and multiple studies over extended periods. For example, qualification of the SV95C outcome in DMD required more than 13 years of research across over ten studies. Achieving full qualification of the digital outcomes presented in this thesis within the timeframe of a PhD was therefore not feasible. Consequently, the results reported should be considered foundational and will require substantial additional research to support regulatory qualification or establish well-validated disease-specific digital outcomes.

Second, part of this work builds on prior research conducted in DMD, which may not be fully generalisable to other conditions. For example, in MS, further investigation is needed to fully explore the potential of wDHT and to identify digital outcomes that specifically capture gait impairment and disease-related mobility changes.

Third, we did not sufficiently examine the patient's perspective. We should address potential issues related to the accessibility of such technology, as not all patients, particularly those with advanced disease, older age or certain socio-economic class, may be equally able or willing to adopt wDHT. The patient's burden should also be considered, as it could affect adherence to device use.

Another limitation is that, while wearable sensors allow for real-world data collection, measurements can still be affected by weather and seasonal variations, device misplacement, or user adherence, which can compromise data quality. Some confounding factors have already been studied in DMD (Rogers et al., 2023). However, we need to assess the generalisability of these findings to the adult population and across conditions.

Finally, this research relied on a single wearable device, which prevented comparisons across different technologies. More broadly, reliance on device-specific algorithms limits the generalisability of our findings and may represent challenges for reproducibility. In this context, greater adoption of open-access approaches, including transparent algorithms and shared datasets, could improve reproducibility, facilitate independent validation, and accelerate the development of digital outcomes across devices and indications. However, several important obstacles limit the implementation of such approaches. First, regulatory restrictions, particularly those related to the General Data Protection Regulation (GDPR), limit data sharing. Even when data are pseudonymised, sharing remains subject to strict conditions and often requires explicit participant consent, which was not anticipated at the time of study design. Fully anonymised datasets may mitigate these concerns, but they often require substantial aggregation or transformation, which can reduce their scientific value and limit the possibility of conducting secondary analyses. Second, important technical challenges must be considered. Raw sensor data generated by wearable devices are extremely large, making their storage and dissemination in open-access repositories difficult. In practice, sharing such datasets would require substantial infrastructure, which are not yet implemented. Finally, intellectual property and financial considerations represent additional difficulties. Algorithms used to derive digital outcomes are often proprietary and developed within academic-industrial partnerships, limiting their accessibility. These constraints may hinder transparency and slow down independent validation efforts. Despite these limitations, efforts should be made to move towards more open and collaborative research practices. This may include the development of standardized data formats to facilitate sharing, the exchange of derived or partially processed datasets, as well as the integration of data-sharing requirements into academic-industrial partnerships, study protocols, and consent procedures. Addressing these challenges will be essential to fully realise the potential of DHTs within an open science context.

II. PERSPECTIVES

Future Data Acquisition and Analysis

A central focus for future work is to expand the dataset to perform further analyses and refinement of algorithms. Many of the results presented in this thesis will require confirmation using independent datasets or over longitudinal periods. Additionally, for PD, findings in controlled environments will need to be validated in real-world settings. For conditions such as MS or ALS, the responsiveness of outcomes to treatment interventions must

be evaluated, which means that these measures should be used as exploratory endpoints in clinical trials. Furthermore, expanding our normative dataset across the ageing adult population is crucial to understand the rate of decline in stride velocity due to normal ageing. This will improve our ability to interpret declines observed in patients with various diseases, particularly in older adults where normal ageing may also contribute to changes in gait. Some of these data are currently being collected.

Furthermore, we also plan to extend the application of this technology to other diseases. We are currently acquiring data on diseases with distal weakness such as CMT disease and DM1 to characterise gait impairment due to distal weakness through wDHT. We also began investigating fatigability in neurological diseases with the goal of identifying an assessment measure that accurately reflects the fatigue experienced by patients. Our initial work focused on MS. However, the complexity of MS and its phenotypic heterogeneity make the assessment of fatigue particularly challenging. In contrast, myasthenic syndromes provide a clear model of muscular fatigability. In this context, we aim to develop a study project on myasthenic syndromes to attempt to identify and validate an assessment measure that could represent fatigue in a population exhibiting pure muscular fatigability without other associated symptoms.

Finally, part of my PhD research was dedicated to a six-year longitudinal study in older patients with SMA receiving newly approved disease-modifying therapies. This cohort provided a unique opportunity to assess the responsiveness of digital outcomes to treatment, even though improvements in this population tend to be milder and less consistent across patients (Iterbeke & Claeys, 2025; Moshe-Lilie et al., 2020) compared with younger patients (Finkel et al., 2025). The analysis of preliminary results has been challenging for several reasons, including difficulties in stride detection in very weak patients and our limited ability to properly assess upper-limb function in non-ambulant patients, as will be discussed in the next section. With the methodological improvements achieved in both domains, particularly the refinement of the stride detection algorithm for patients with ALS, we are currently reanalysing the data, having just completed the final phase of data collection. Moreover, many patients qualitatively reported increased endurance and reduced fatigability, and they will be included in our upcoming fatigability analysis. This work is currently ongoing and, unfortunately, could not be included in the present manuscript.

Technical Progress

An important next step is to leverage the data collected throughout this work to develop novel digital outcome measures. Rather than focusing on already established gait metrics, future efforts should aim to derive more specific measures that capture distinct clinical features, such as ataxia, fatigability, or stiffness. In addition, certain metrics may need to be tailored to specific populations, accounting for age-related changes and disease-specific characteristics. This approach acknowledges that a single set of outcomes is unlikely to be universally applicable across heterogeneous neurological conditions. Instead, the development of targeted, symptom- or population-specific metrics may improve sensitivity to clinically meaningful changes. It may also facilitate the evaluation of treatment responses, particularly for interventions targeting specific aspects of a disease (e.g., the use of baclofen

to reduce spasticity in various neurological conditions). Ultimately, this approach could broaden the applicability of digital measures in both research and clinical contexts.

Although not exhaustive, the following section presents selected examples of candidate concepts of interest and methodological approaches that may support this objective.

Algorithm Refinement for Fatigue

Fatigue is a complex, multidimensional symptom that is particularly challenging to quantify by using clinical assessment. Although wDHT enables continuous data collection and could theoretically support an improved characterisation of fatigue, its quantification remains as difficult. To address this challenge, we explored multiple strategies to develop fatigue-related digital metrics.

First, because fatigue is often characterised by declining performance over time, such as reduced movement quality (e.g., slower walking velocity, increased stride variability) or decreased activity intensity (e.g., step count), we compared sensor-based mobility features collected in the morning versus in the afternoon. At this stage, this approach does not appear promising, particularly for physical activity measures, which are largely driven by external factors.

Second, we evaluated gait features following periods of intense locomotor activity. Specifically, we identified high-intensity walking episodes from continuous recording data and performed targeted extraction around these episodes. Temporal segmentation was implemented around each participant's peak activity windows. Movement features extracted during these high-activity periods were compared with those from surrounding time periods to characterise exhaustion and recovery dynamics. The goal was to determine whether transient post-exertional decline could serve as a proxy for fatigability. This approach, however, raised several methodological challenges: defining what constitutes high-intensity exertion (e.g., activity intensity alone versus intensity sustained over duration), selecting appropriate thresholds, and adapting these thresholds to individual impairment levels. Notably, what qualifies as high intensity likely varies substantially across patients. Additional challenges include defining the onset and duration of recovery periods and identifying which parameters most accurately reflect fatigability.

This strategy may ultimately improve the ability of digital outcomes to assess fatigue and fatigability. Future work will focus on a cohort of patients with myasthenic syndromes. In this population, we will also consider integrating structured tasks to standardise exertion levels, more clearly define recovery periods, and identify parameters that best represent fatigability.

Algorithm Refinement for Upper Limb Analysis

Specific algorithm refinements have been discussed separately in each chapter of this manuscript. However, a general consideration is the need to focus on upper limb evaluation. Assessing the upper limbs using wDHT is

more complex than gait assessment due to gyroscope drift which refers to the gradual accumulation of error in angular velocity measurements over time, especially during long-term recordings without correction.

The drift poses greater challenges for upper-limb assessments than for lower-limb assessments, as the upper limbs lack consistent external reference points that can be used to recalibrate gyroscope data. In gait analysis, the lower limbs naturally provide opportunities for drift correction, as each step includes brief moments of foot contact with the ground, allowing algorithms to reset accumulated drift. By contrast, arm and hand movements are highly variable and task-dependent, without predictable periods of rest or stable reference positions. As a result, simple correction strategies are difficult to apply, and measurement accuracy depends on advanced software or contextual task information with the latter often not being available in real-world monitoring.

Furthermore, the lack of repetitive movements in the upper limb, unlike strides in the lower limb, makes it challenging to identify reliable outcome measures that are not influenced by passive motion or other confounding factors. In lower-limb assessment, strides can be accurately detected and external or aberrant movement detection filtered, which is not possible in upper-limb evaluation.

Despite these many challenges, validating upper-limb outcome measures remains essential for monitoring patients throughout disease progression, including during the loss of ambulation. It will also enable the inclusion of non-ambulant patients, who are too often excluded from participation, in clinical trials. Achieving this level of technical advancement will require the integration of ML and AI.

The role of Artificial Intelligence and Machine Learning

While AI, ML, and wDHT are distinct fields, they can be used together to amplify the potential of wDHT. AI and ML could dramatically enhance the value of wDHT by transforming raw longitudinal sensor data into clinically meaningful outcomes. While wDHT focuses on the collection of continuous data, AI and ML are concerned with developing algorithms and models that learn from these data. Using the large volumes of data generated through continuous monitoring, AI and ML could provide predictive insights (Kadirvelu et al., 2023), support earlier and more accurate disease diagnosis (di Biase et al., 2024) and guide personalised treatment planning.

Recent studies demonstrated how combining wDHT with ML can overcome traditional clinical scales. For example, in DMD, ML-derived “ethomic” fingerprints movement predicted functional scores and disease trajectories more accurately than standard assessments (Ricotti et al., 2023). This approach ultimately aims to identify digital metrics capable of tracking disease progression along a sigmoidal trajectory. Such a trajectory differs markedly from the inverse-U shape observed in currently used outcomes, where apparent early improvement is largely driven by normal growth and child development rather than true disease stabilisation, masking the underlying continuously progressive nature of the disorder.

Similar approaches in FRDA showed that ML models trained on kinematic metrics could predict patient-level Scale for the Assessment and Rating of Ataxia (SARA) and Spinocerebellar Ataxia Functional Index (SCAFI) scores up to nine months ahead and provided substantially higher predictive precision than clinical scales. Furthermore, digital

behaviour features could predict FXN gene expression levels. In a cohort of 76 individuals with SCA and MSA, ML-derived outcomes demonstrated strong correlations with clinician-rated and patient-reported scales, high effect-size group separation from controls and excellent reliability (Manohar et al., 2025). In the same study, longitudinal analyses revealed significant sensitivity to change over time with an ALS-trained model showing the highest responsiveness, despite being trained in a different disease population.

In ALS, real-life monitoring with wDHT combined with ML produced composite severity scores that progressed faster than the ALSFRS-R, reducing required clinical-trial sample sizes (Gupta et al., 2023).

These examples illustrate how AI/ML can extract clinically relevant signals beyond traditional human-defined measures, allowing more sensitive detection of disease change, reduction of trial duration and sample size. However, AI/ML-derived digital biomarkers are not always directly interpretable.

As defined in the introduction, interpretability refers to the extent to which qualitative meaning can be assigned to quantitative scores (Mokkink et al., 2010). Interpretability is critical not only for assessing the true impact of a treatment on patients but also for regulatory and reimbursement purposes. Payers and healthcare providers need to understand the expected benefits to approve therapies or reimbursement. Without clear interpretability, regulators, payers and clinicians may also be reluctant to rely on metrics derived from AI/ML models for treatment decisions.

Therefore, digital biomarkers generated via AI/ML are currently most likely to be adopted for early-phase research, diagnostic support, risk stratification, or exploratory secondary endpoints, rather than for pivotal phase III primary outcomes or routine clinical decision-making. As methodological and regulatory frameworks evolve, it is likely that different types of outcomes, with distinct purposes and origins, will emerge in the coming years.

Emerging Applications: Immediate Opportunities and Future Possibilities

While much of the following is purely hypothetical and remains to be demonstrated, wDHT shows a significant potential of development in several domains of healthcare.

In clinical research, this technology has already shown promises by demonstrating their potential to shorten trial duration and reduce the number of participants required in trial cohorts. For example, the SV95C is already being used as an outcome measure in several interventional trials in DMD (NCT05096221, NCT04906460, NCT07160634, NCT06138639, NCT05524883) but also in other neuromuscular disorders (NCT06747273, NCT06952686). Furthermore, this approach could help identify highly sensitive outcome measures that guide the transition from Phase II to Phase III studies, enable precise patient stratification, and optimise trial design. Achieving this level of sensitivity, particularly when strong interpretability is not mandatory, would likely require an AI/ML approach, as outlined above. Together, these applications have the potential not only to increase the efficiency and accuracy of clinical trials but, more importantly, to accelerate the overall process of drug development.

This same technology could also be used for monitoring as part of standard care, enabling the assessment of therapy response in an objective and highly sensitive manner. It could be particularly valuable for conditions in which variability is a key feature of the disease phenotype and where in-clinic assessments may not accurately reflect the patient's true health status, such as PD or MG. It could also be transformative in populations that are unable to provide reliable traditional assessments, such as very young patients or those with cognitive or developmental disorders. Additionally, it could provide tremendous support in diseases like chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), where traditional assessment methods often fail to deliver an objective picture, potentially compromising both clinical trial outcomes and treatment adjustments in everyday clinical practice (Adrichem et al., 2022; Mahdi-Rogers et al., 2009). In the context of our work, for diseases in which we can collect sufficient longitudinal data, such as DMD, it becomes possible to apply statistical methods to predict an individual patient's trajectory. Indeed, these models can generate an individualised prediction of how a patient is expected to decline over time without intervention. Once a predicted trajectory is established, clinicians can compare it to the patient's observed progress while receiving treatment. If the patient's real-world data show slower disease progression or functional improvement compared with the predicted trajectory, this may help clinicians to more sensitively determine whether a treatment is effective at the patient's level. Furthermore, thanks to the sensitivity of digital outcome for subtle change in gait, they could serve not only for detection of disease progression, but they could also support earlier and more accurate disease detection, allowing clinicians to identify conditions at stages when interventions are most effective. To achieve this, extensive validation work would be required. In addition, substantial improvements in access to these devices and to the results they generate, as well as appropriate training for patients, caregivers, and clinicians in their use and interpretation, would be necessary.

III. CONCLUSION

In the rapidly evolving field of digital neurology, wDHT represents a promising approach in both research and clinical care. While many challenges remain, the potential of wDHT to improve disease monitoring is huge. I am deeply convinced that continued innovation and collaborative efforts will undoubtedly yield significant scientific advancements in the years to come.

3

PART 3

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4

PART 4

APPENDIX

APPENDIX 1

LIST OF PUBLICATIONS

I. SCIENTIFIC JOURNALS

Poleur, M., Willekens, B., Degos, B., Ricard, D., van Pesch, V., Mélin, A., Piquet, O., Tricot, A., Médard, L., Michaud, M., Lommers, E., De Keersmaecker, A.-V., Coman, I., Overell, J., Goodyear, A., Delmar, P., Wang, Q., Hayward-Koennecke, H., Cluzeau, C., ... Servais, L. (2026). Stride-level measurement of gait as an early sensitive marker of disability progression in ambulatory patients with multiple sclerosis. *EClinicalMedicine*, 93, 103823. <https://doi.org/10.1016/j.eclinm.2026.103823>

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Servais, L., Strijbos, P., Poleur, M., Mirea, A., Butoianu, N., Sansone, V. A., Vuillerot, C., Schara-Schmidt, U., Scoto, M., Seferian, A. M., Previtali, S. C., Tulinius, M., Nascimento, A., Furlong, P., Singh, T., Dreghici, R. D., Goemans, N., Mercuri, E., Straub, V., ... Eggenspieler, D. (29 November 2024). Evidentiary basis of the first regulatory qualification of a digital primary efficacy endpoint. *Scientific Reports*, 14 (1), 29681. doi:10.1038/s41598-024-80177-9. <https://hdl.handle.net/2268/324960>

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II. CONGRESSES AND SYMPOSIA

Articles Accepted in Conference Proceedings

Poleur, M., Parinello, G., Vrščaj, E., Kumhera, M., Bisson, C., Aragon-Gawińska, K., Anghelescu, C., Daron, A., Szabo, L., Leanca, M., Mirea, A., Kodsy, S., Saleh, A., Osredkar, D., Haberlova, J., Potulska-Chromik, A., Butoianu, N., Eggenspieler, D., Strijbos, P., & Servais, L. (October 2024). 400P Longitudinal evaluation of ambulatory function with ankle wearable technology in ambulant DMD. *Neuromuscular Disorders*, 43, 104441.128. doi:10.1016/j.nmd.2024.07.137. <https://hdl.handle.net/2268/327864>

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Oral Presentation

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Poster Presentation

Tychon, C., Poleur, M., & Servais, L. (14 March 2025). Walking speed during daily living, a systematic review [Poster presentation]. BAoP Congress, Mons, Belgium. <https://hdl.handle.net/2268/3305842024>

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