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

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The development of effective therapies is contingent on the ability to detect the effects of treatment on disease progression. This is particularly challenging for neurological diseases, for which objective and robust endpoints that measure functional disease progression are often lacking, reducing the probability of technical and regulatory success for new treatment options. Reliable and sensitive digital outcome measures that continuously assess functional ability during normal daily life can revolutionize the evaluation of disease progression and facilitate drug development. The first-ever regulatory qualification of a digital variable, the stride velocity 95th centile (SV95C), as a primary endpoint by the European Medicines Agency (EMA), represents a landmark event that establishes the value of digital health technology and endpoints for drug approval.

Duchenne muscular dystrophy (DMD) is a rare monogenic disease that causes progressive loss of muscle function and premature death. Despite extensive research and development efforts, DMD remains the leading cause of severe disability and early death in boys with monogenic muscle disorders, highlighting the need for new treatment options[1,2].

The urgent need for disease-modifying therapies has motivated stakeholders to develop new trial methodologies, including research on individual patient trajectories[3] and external control data[4]. Although impactful, these innovations rely on the ability to measure a disease state accurately and objectively, and require relatively large patient numbers owing to variable clinical progression.

Established methods for measuring functional disease progression in pivotal DMD clinical trials include performance-based tests and multidomain assessment scales, which require investigators to administer tests and patients to actively participate in the clinic. Examples include the 6-minute walk test (6MWT), the four-stair climb test, and the North Star Ambulatory Assessment.

Although these assessments are validated and considered suitable for drug approval, they have important limitations; patients with DMD may exhibit attention deficits[5] and/or psychomotor delays[6], which could affect assessment reliability. Moreover, these tests are influenced by variables such as motivation and fatigue[7]. Hence, trials in DMD are typically long and require large numbers of participants to detect meaningful treatment benefits. These challenges are exacerbated in trials of rare diseases, which often have limited numbers of geographically dispersed participants, potentially introducing bias due to variable standards of care.

When designed to be fit-for-purpose, digital health technology offers unique opportunities to develop functional endpoints that are less susceptible to these pitfalls. These include wearable devices that allow continuous and objective collection of accurate and
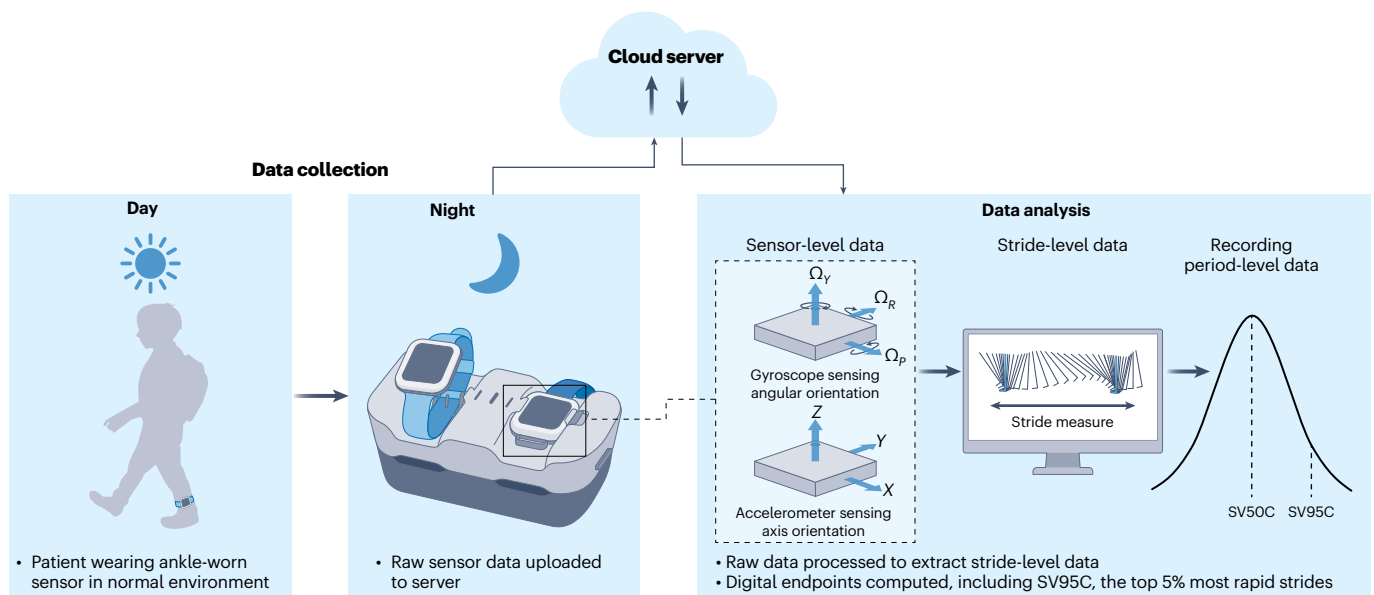

Fig. 1 | Data collection and analysis using SV95C. Raw sensor data are collected by an ankle-worn device continuously throughout the day. At night, the patient or caregiver places the sensor on a docking station that transfers the encrypted and anonymized data to a secure web cloud. Data are accrued over several days to reach the minimum threshold of 50 hours over a duration (known as the recording duration) defined in the study protocol and monitored regularly. The data are processed to extract stride-level data and compute digital endpoints, including the stride velocity 95th centile (SV95C). SV50C, stride velocity 50th centile.

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meaningful patient data in a natural environment. These types of high-sensitivity data may support regulatory decision-making and benefit patients, families and the scientific community[1]. For example, remote monitoring benefits patients living far from investigational sites or those for whom in-person assessment poses risks, such as during the COVID-19 pandemic.

The original use of digital technology in DMD research involved sensors for measuring basic quantitative outcomes, such as step count or the number of steps taken[8]. However, these outcomes are highly variable, as they are influenced by factors unrelated to disease progression, such as the weather.

Some qualitative outcomes are less affected by such factors. One example is SV95C, a new digital endpoint representing the top 5% fastest steps taken during normal daily living[9] over a pre-defined duration (Fig. 1). The 95th centile reflects an intense activity level that is sensitive to disease progression and treatment effects without the interference of external circumstances in daily life, and the pre-defined duration limits the effect of periodic fluctuations, such as the time of day. Compared with step count, for example, the SV95C of patients with limited ambulatory ability is less dependent on external factors and thus more objectively reflects disease progression.

Fit-for-purpose wearable sensors, such as those that measure SV95C, also present the opportunity to measure additional relevant outcomes, including fatigability and balance — which can be used as secondary or tertiary endpoints to quantify other aspects of disease progression or therapeutic intervention.

There are substantial hurdles to developing wearable technology and digital endpoints suitable for clinical research. These include the technical and analytical validation of the digital health technology; the need for substantial, diverse normative and patient data; geographic differences in data protection legislation and local device certification requirements; technical challenges of collecting data in an uncontrolled environment; the qualification procedure itself; and patient compliance with wearable devices. However, despite the logistic difficulty of ankle-worn devices for some patients, patient compliance with wearing the Syde device (a new form factor of ActiMyo) used to qualify SV95C in clinical trials was typically excellent[9].

In 2019, the EMA qualified SV95C for use as a secondary endpoint in pivotal studies of DMD in patients aged at least 5 years[9]. SV95C was developed through a DMD community effort that facilitated the validation and adoption of the endpoint. SV95C is broadly used in clinical trials (for example, ClinicalTrials.gov identifiers NCT05096221, NCT03039686 and NCT03907072) to measure real-world functional disease progression as a complement to in-clinic assessments.

Recently, SV95C was approved by the EMA for use as a primary endpoint in pivotal trials of DMD, representing the first-ever qualification by a regulatory agency of a digital endpoint for use as a primary endpoint for any indication[10]. The EMA final qualification opinion stipulates that SV95C be measured by an ankle-worn device meeting certain technical specifications.

As described by the EMA, SV95C has appropriate metric properties. SV95C has been validated based on all three levels of the V3 framework: verification (high measurement reliability; intraclass correlation coefficient: 0.937)[9,10]; analytical validation (SV95C correlates with established ambulation measures, including the 6MWT; Spearman's rho: 0.657)[10]; and clinical validation (SV95C can discriminate patients with DMD from age-matched controls and is highly sensitive to functional change; 1-year standardized response mean: 0.87 versus 0.78 for the 6MWT)[10].

The ground-breaking EMA qualification of SV95C as a primary endpoint is likely to transform drug development in DMD by enabling shorter trials with smaller patient numbers. Considering the need for objective and sensitive endpoints in other rare neuromuscular diseases, the collection of digital endpoint data with fit-for-purpose technology has the potential to revolutionize and simplify drug approval for other therapy areas. This qualification demonstrates that regulatory bodies will consider digital endpoint data collected with fit-for-purpose technology for drug approval purposes, setting an important regulatory and industry precedent for the development and use of high-sensitivity digital endpoints in clinical trials.

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Competing interests

L.S. has conducted consultancy and given lectures for F. Hoffmann-La Roche Ltd, Sarepta Therapeutics, Santhera Pharmaceuticals, Pfizer, Dyne, RegenexBio and SYSNAV. D.E. is an employee of SYSNAV. M.G. is a former employee of SYSNAV. F.M. has conducted consultancies and given lectures for F. Hoffmann-La Roche Ltd, Sarepta Therapeutics, Santhera Pharmaceuticals, Eli Lilly and Company, Pfizer, Wave Life Sciences Ltd, PTC Therapeutics and Dyne Therapeutics. P.S. is an employee of and holds stock in F. Hoffmann-La Roche Ltd. M.A. is an employee of SYSNAV. M.P. declares no conflicts of interest.