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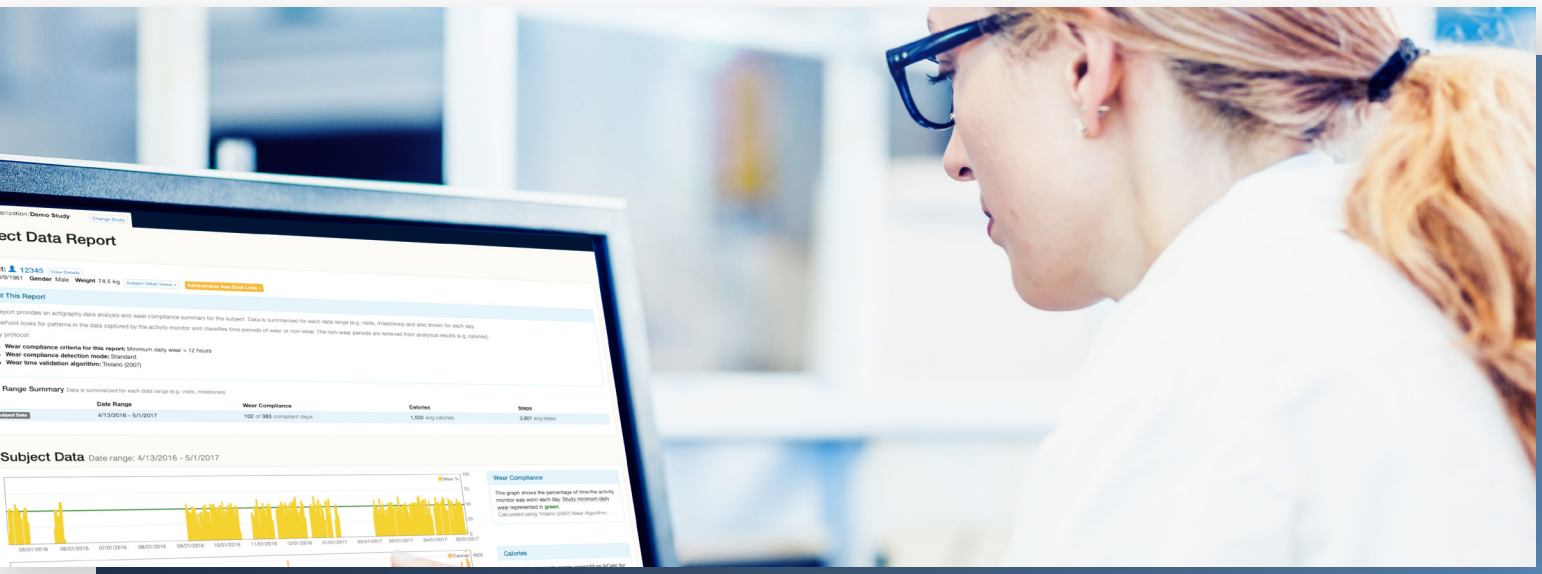
eBook

A Guide to Wearable-Enabled Digital Clinical Measures in Neuroscience

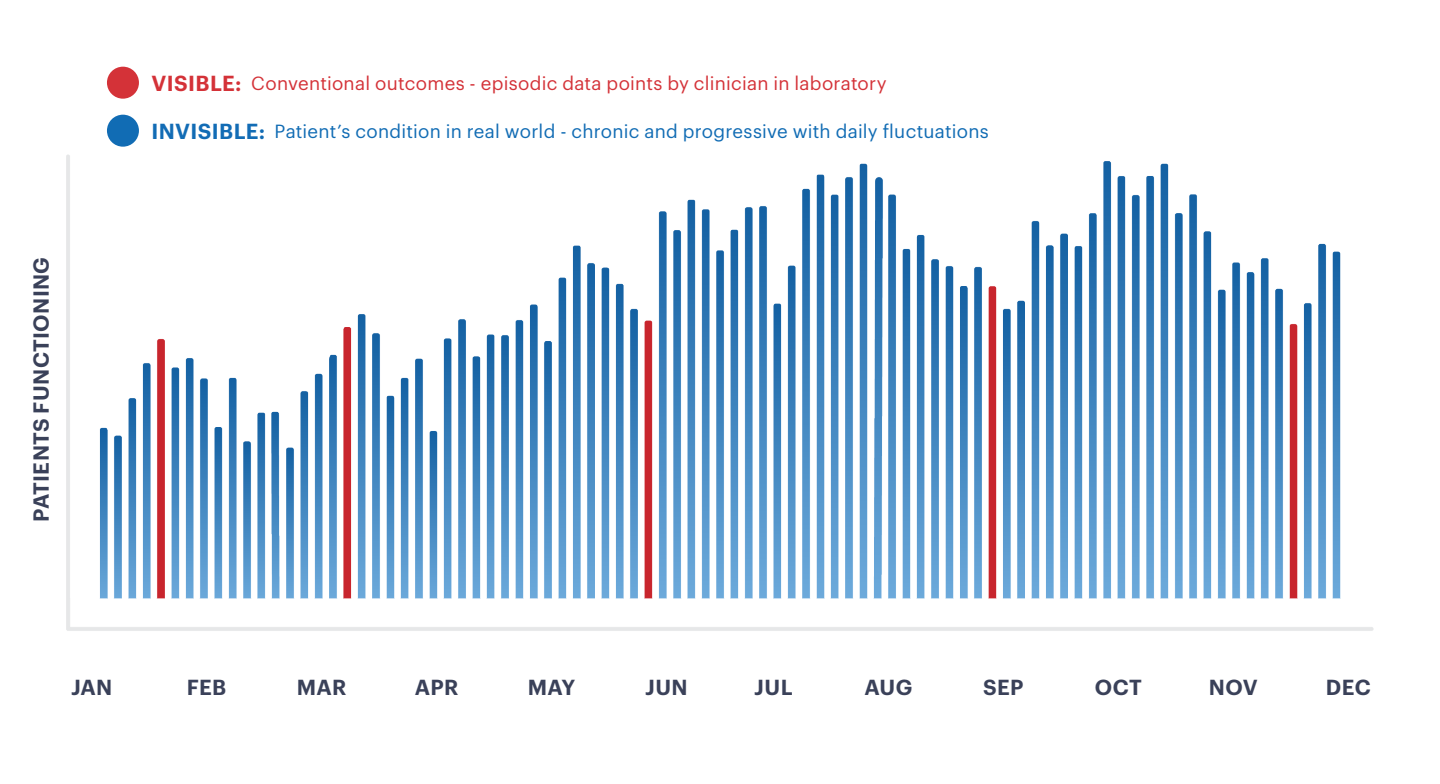
Table of Contents



Introduction

Drug development in neurology is notoriously challenging. Despite being one of the most active areas of clinical development, neurological disease drug trials have among the longest development timelines and highest failure rates in the industry.[1] This poor track record reflects the complexity of the nervous system and the lack of mechanistic understanding of neurobiology in humans. Imprecision in both disease diagnosis and symptom monitoring presents additional hurdles for clinical development.

Neurological diseases are inherently complex, manifesting a variety of motor and non-motor symptoms. This complexity, combined with slow progression and symptom fluctuation, impedes the accurate assessment of disability and disease progression. Traditional measures based on subjective rating, either by clinicians or patients, are susceptible to rater bias and are often sampled between long intervals of time. These clinical measures do not capture subtle changes in neurological function and fail to reveal the full picture of disease progression.



Digital clinical measures enabled by wearables have great potential to transform and accelerate drug development in neuroscience. Digital assessments of function, as quantified from smart sensor data, can provide frequent, objective, and precise measures of how participants function in their real lives. In particular, wearable devices collect continuous digital data remotely and passively, thus improving patient-centricity and reducing trial burden on patients. As clinical conditions in neuroscience are often debilitating and chronic, low burden trial designs are key to the success of trial recruitment and completion.

Outcome assessments based on real-world activity and function are well aligned with regulators' emphasis on meaningful aspects of health and patient-centered drug development. Wearable-enabled digital measures of mobility and gait have been accepted and favored by the European Medicines Agency (EMA) as secondary endpoints in several neurological conditions.[2] The U.S. Food and Drug Administration (FDA) has also endorsed the use of physical activity measures based on ActiGraph technology as primary endpoints, albeit not in neuroscience.[3] With appropriate levels of validation, wearable-enabled digital endpoints could accelerate development of the right treatments for patients living with neurological and psychiatric conditions.

Special Operational Considerations in Neuroscience

Clinical trial participants with impaired motor and/or cognitive function are likely to have some difficulties handling and using wearable devices, especially if they are foreign or complex in nature. In some cases, a spouse or caregiver might need to provide assistance. A wearable that is simple to put on and which requires minimal interaction, such as battery charging, is less burdensome to the participant. Additionally, study designs with constant data collection are particularly well suited to populations with memory problems. This allows participants to become familiar with the technology and reduces non-adherence due to forgetfulness. With careful deployment, high adherence for passive monitoring with wrist wearables has been demonstrated, with one study reporting that subjects wore the device during 94% of the requested wear periods.[4,5] Usability and operational simplicity have been found to impact adherence significantly, especially in populations with cognitive impairments.[6]

When conducting a clinical trial on challenging populations, real-time monitoring of participant adherence should be of the highest priority. It is important to ensure that technical issues with data collection and upload do not confound adherence monitoring. For example, BYOD (bring your own device) approaches could be problematic in this respect, especially in countries where unlimited cellular data plans might not be commonplace. Dedicated wearable devices and data plans are likely to be more robust with minimal burden to the patients.

Movement Disorders

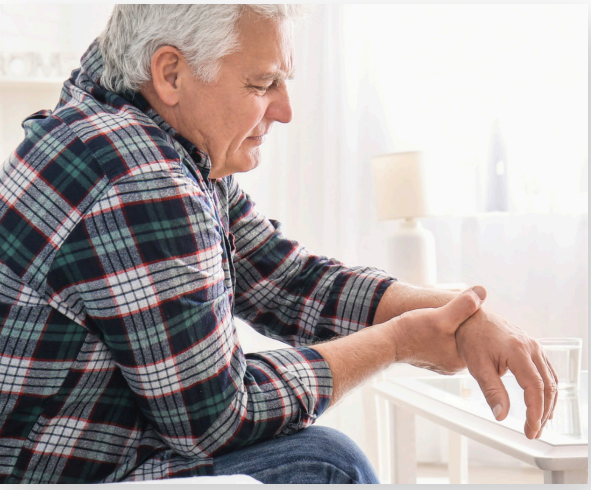
Movement disorders, such as Parkinson's disease (PD), Huntington's disease (HD), essential tremor, and ataxia are characterized by complex motor symptoms. Frequent fluctuations and a high degree of variability in these motor symptoms make it difficult to capture reliable outcome assessments via traditional approaches. Wearable sensors, especially inertial measurement units (IMU), are well suited to assess these complex symptoms with quantitative, high dimensional motion analysis.[7] Wearable-enabled assessments can collect data continuously 24-7 in the participants' everyday life, minimizing the impact of sampling and contextual bias on outcome assessments.

Gait and Posture

People with movement disorders often suffer from deficits in their ability to walk and balance. With wearable devices, gait and balance can be assessed and monitored, not only during supervised tests in the clinic, but also continuously during real-life walking episodes.[8,9] Freezing of gait during real-life events is of particular interests to clinical development in PD.[10] Quantitative and objective assessments of gait and posture could reveal very subtle changes in gait characteristics that might not be obvious otherwise – sometimes many years prior to clinical diagnosis.[11] Furthermore, detection of falls and fall risks in real life is another area where wearables can provide valuable information to the clinical care of people with movement disorder.[12,13]

Tremor, Dyskinesia, and Other Motor Symptoms

Wrist-worn wearable devices are well suited to quantify tremor and dyskinesia of the upper limb. Not only can they track those symptoms and their fluctuations continuously in real life,[14] but they can also be used to differentiate between different types of tremors.[15] In addition, wearables can diagnose and monitor hallmark motor symptoms such as parkinsonism in PD and chorea in HD.[7]



Beyond quantifying specific gait and motor symptoms, wearables can also offer insights into general quality of life through objective assessments of physical activity and sleep. The high quality and high dimensionality data offered by wearables have great potential to advance the early and accurate diagnosis and continuous real-world monitoring of disease progression, consequently accelerating drug development in movement disorders.

Physical Activity and Functioning

Compared to the healthy population, individuals with movement disorders tend to have a more sedentary lifestyle, spending less time in high intensity activity and more time in sedentary and light intensity activity.[16] Ability to exercise and stay active is an important aspect of the quality of life and well known to be beneficial to disease management. Compared to patient reports, wearable devices can provide a more objective and accurate assessment of physical functioning in the real life, which has been shown to reveal aspects of disability that are not be covered by traditional clinical assessments.[17]

Sleep

Sleep is another important aspect of health to people with movement disorders. Sleep represents the second most common non-motor complaint among patients with PD. In a large survey study, 64% of patients with PD reported sleep problems,[16] and sleep can become impaired at a very early stage of the disease.[18] Sleep interruptions and turns, quantified by wearable accelerometers, showed differences between individuals with advanced PD, early PD, and without PD, supporting the use of sleep metrics as objective measures of disease severity.[19] In fact, actigraphy-based sleep measures have been used as efficacy endpoints and shown treatment effect in randomized control trials in PD.[20]

Neurodegenerative Disorders

Clinical trials in neurodegenerative disorders like Alzheimer's disease (AD) and dementia are increasingly focusing on early intervention and/or prevention in prodromal individuals. This poses a great challenge on the sensitivity of the efficacy endpoints, as existing endpoints are often unable to detect cognitive and functional changes at the very early stages of disease. Several large-scale AD cohort studies have incorporated wearables to assess the feasibility and validity of digital measures for the early detection and monitoring of disease progression.[21]

Gait

Gait impairments are well recognized in AD, but they had previously been thought to only occur in advanced stages of the disease. Recent evidence, however, suggests that motor and sensory function are affected very early, preceding signs of cognitive impairment by at least a decade.[22] Accordingly, quantitative gait analysis has demonstrated gait abnormalities in people with AD or the prodromal stage (MCI), including reduced stride length and cadence, and greater stride-to-stride variability.[23] Gait speed, in particular, was found to exhibit accelerated decline up to 12 years before the diagnosis of MCI.[24]

Sleep

Sleep disturbance is another common symptom in patients with AD. Among the types of sleep disturbance often reported in this population, circadian rhythm disorders are the most frequent.[25] Circadian rhythm disorders can be aggravated by behavioral and psychological symptoms of dementia, such as wandering at night and agitation. However, assessing sleep patterns remains challenging in dementia because cognitive impairments often confound the validity of traditional self-report sleep questionnaires. Wearable devices that are low burden with minimal obstruction to the participants' life present an attractive solution to monitoring sleep disturbances in AD and neurodegenerative diseases. Actigraphy-derived sleep measures detected significant treatment responses to a novel brain stimulation therapy in a recent PhI/II RCT study, corroborating improvements in Activity of Daily Living.[25]

Physical Activity and Functioning

Evaluating an individual's activity levels and intensity has been shown to be correlated with several different biomarkers related to the onset or progression of AD and dementia. For older, cognitively healthy subjects, a higher amount of moderate intensity activity was associated with a favorable AD biomarker profile, while higher sedentary levels were associated with higher amyloid ß plaques.[26] In addition, time spent in moderate activity is also associated with cerebral glucose metabolic rate in multiple areas of the brain for the same cohort.[27]

Neuromuscular Disorders

Neuromuscular disorders (NMD) refer to a heterogenous group of clinical conditions that affect the function of muscles due to problems with the nerves and muscles. People with NMD typically suffer from muscle weaknesses throughout the body. However, the severity and progression can vary greatly, even among individuals with the same diagnosis, imposing challenges to NMD drug development. Most NMD are rare diseases without disease modifying therapies, where established clinical outcome assessments might not exist. Although this creates challenges to clinical development in NMD, it also presents an opportunity for the acceptance and adoption of novel digital clinical outcomes.

Gait

The first qualification of a novel digital endpoint by a major regulatory body occurred for Duchenne Muscular Dystrophy (DMD).[28] European Union regulators accepted stride velocity 95th centile as an acceptable secondary efficacy endpoint in clinical trials of ambulant DMD patients. While this outcome is still under consideration by the FDA, this acceptance marks a major milestone for the use of digital endpoints to demonstrate clinical benefit of therapy and the use of real-world gait speed as functional outcomes in NMD.

Upper Limb Function

Wearables can provide continuous assessments of upper limb function and gross motor skills in real life. This is of particular importance for NMD where many patients lose the ability to walk. A variety of accelerometry-based variables of upper limb activity could be useful in identifying impairments and/or monitoring treatment outcomes.[29] To fully examine upper limb function, two devices might be needed, especially if the concept of interest entails the ratio or asymmetry between two arms.[30] Overall, it is important to identify digital measures that reflect functions that are meaningful to the participants and can be assessed reliably in the real-world environment.

Physical Activity and Functioning

Digital measures of physical activity and functioning are key to understanding the functional capacity of people living with NMD in their everyday life. In a fully-remote study in amyotrophic lateral sclerosis (ALS), digital endpoints based on wearables are highly feasible with an adherence rate of 93% and were strongly associated with longitudinal disease progression as assessed by ALS Functional Rating Scale.[31] Statistical modeling further showed that digital endpoints could reduce sample size by 30.3% for 12-month trials and by 44.6% for 18-month trials. Remote assessments using wearables substantially reduce the barriers of study participation, leading to greater success in trial recruitment and completion in these highly debilitating conditions.

Psychiatric Disorders and Chronic Pain

People living with mental illnesses, such as schizophrenia and major depressive disorder (MDD), as well as chronic pain have shown changes in physical activity and sleep associated with their clinical conditions.[32,33] Due to cognitive impairments typically observed in these populations, it can be challenging to assess true treatment effects using patient-reported outcomes. Wearables thus provide a powerful and useful tool to objectively measure clinical outcomes in clinical trials.

Physical Activity, Functioning, and Sleep

Physical activity and sleep provide important insights into the quality of life for people living with mental illnesses or chronic pain. These populations generally have lower activity levels and poorer sleep quality compared to healthy controls. Lower physical activity and longer sleep duration can also be an indicator of increased severity of negative symptoms in people with schizophrenia.[34] Less structured physical activity and decreased sleep quality can be associated with greater severity of positive symptoms and lower quality of life for those individuals as well. In a qualitative interview study, many caregivers reported that outcomes that improved sleep, exercise, and physical activity were important.[35]

In chronic pain, physical functioning is identified as a core outcome domain and key assessment for treatment efficacy.[36] Compared to conventional clinical outcomes of physical functioning, wearable-enabled measures can provide much richer insights into how individuals with chronic pain function physically and potentially respond to treatments in their daily life. People with chronic pain identified sleep as one of the most important aspects of their lives where they would like to see improvement.[37]

Conclusion

The use of wearable-enabled digital measures has the potential to transform and accelerate clinical development in neuroscience, one of the most active and notoriously challenging areas of research. The evidence presented here illustrates how wearable-derived digital endpoints can be used to quantify motor symptoms, assess disease progression and severity, and provide insights on the quality of life across a variety of neurological and psychiatric diseases.

Use of digital endpoints for proof of clinical benefit in phase II trials could potentially reduce the uncertainty of Phase II-Phase III transition and improve the probability of success in Phase III studies. Digital endpoints that are more sensitive to disease progression could substantially reduce the cost and timeline of Phase II and Phase III trials.

ActiGraph is passionate about expanding the use of digital endpoints to advance the treatment options that are beneficial to patients. We believe in future-proof raw data generation, fit-for-purpose algorithms and a systematic research framework following regulatory and industry standards.[38] We partner with industry and academic researchers to develop and validate fit-for-purpose digital endpoints and bring them to real impact in clinical development.

ActiGraph™

ActiGraph is pioneering the digital transformation of clinical research. We provide end-to-end digital health technology (DHT) solutions by integrating and operationalizing the best hardware, software, and algorithms to generate reliable evidence and get the right treatments to the right patients, faster. ActiGraph's medical-grade wearable technology platform has been used to capture real-world, continuous digital measures of activity, sleep, and mobility for nearly 250 industry-sponsored clinical trials and thousands of academic research studies. Appearing in over 22,000 published scientific papers to date, ActiGraph is the most experienced and trusted wearable technology partner in the industry.

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