

Implementing Wearable Technologies to Measure Clinical Outcomes in Multiple Sclerosis:

A Scoping Review

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Wearable technology refers to any sensor worn on the person, making continuous and remote monitoring available to many people with chronic disease, including multiple sclerosis (MS). Daily monitoring seems an ideal solution either as an outcome measure or as an adjunct to support rater-based monitoring in both clinical and research settings. There has been an increase in solutions that are available yet there is little consensus on the most appropriate solution to use in either MS research or clinical practice. We completed a scoping review (using the PRISMA-ScR guidelines) to summarise the wearable solutions available in MS in order to identify those approaches that could potentially be utilised in clinical trials, by evaluating: scalability, cost, patient adaptability and accuracy. We identified 35 unique products that

measure gait, cognition, upper limb function, activity, mood and fatigue with most of these solutions being phone applications.

Key Words: Multiple Sclerosis, Wearable Technology, mHealth, Biosensors, remote sensing technology, mobile applications

Introduction:

Assessment of new treatments in multiple sclerosis (MS) studies necessitates effective, reliable, and validated outcome measures. Most clinical MS outcome measures are rater-dependant and are applied episodically.¹ Clinical trials in MS require sensitive outcome measures, that can detect small changes in disability or functional improvement on a frequent basis, which can then reliably reflect long term changes.²

With the advances in technology over the last few decades, it is now possible to explore methods of accurate, sensitive and objective continuous remote monitoring.^{3,4} Wearable technology, otherwise often referred to as biosensors or smart sensors, are mobile technology solutions that can be worn by the person and often include passive or active tracking capabilities which can be used to assess health and well-being.⁵ Common examples of these devices include the FitBit® activity band and smartphone applications like MapMyRun®. Advancements in wearable technology and phone applications (“apps”) enable continuous patient-based monitoring and provide feedback on daily life. The results of daily monitoring using wearable technology could be used either as an outcome measure or as an adjunct to support rater-based assessments. There has been an increase in solutions that are available for those who are diagnosed with chronic illness, especially in regards to neurological disease.⁶ Yet, there is little consensus on the most appropriate solution to use in either MS research or clinical practice.

Studies, have shown that patients, caregivers, and healthcare professionals find value in using such devices especially when they are less-invasive in day-to-day situations and provide real-time feedback.^{7,8} Currently, there are no published randomised control trials (RCTs) that have utilised wearable technology in PwMS, however there are several RCTs currently on-going that utilise wearable technology, for example, the MD3001 (SPI2) trial.⁹

The advantages and disadvantages of wearable technology are summarised in the table below.

Table 1: Potential advantages and disadvantages of wearable technology in trials

Advantages	Disadvantages
Continuous or frequent monitoring	Cost of device
Remote monitoring ability	Secure data storage
Less invasive	Local skin irritation
Decreased travel burden for participants	Troubleshooting device
Feedback to the participant	Charging and battery life of devices
Ease of use	Software upgrade incompatibility

The rationale for conducting this scoping review was to understand each solution and their utility in multiple sclerosis. This review was commissioned by the Outcome Measures working party as part of the Expert Consortium on Progression in MS Clinical Trials, which is a UK MS Society initiative. We reviewed wearable technology solutions with a particular interest in their potential to detect changes in function for PwMS in a more reliable and accurate manner, and their suitability for use in a UK wide multi-centre platform trial.

Objective:

To identify all validated wearable solutions for PwMS and determine suitability for use in a UK wide multi-centre platform trial by considering the following factors; reproducibility in MS populations, feasibility (including cost), patient adaptability and prior use in an RCT.

Methods:

We used a scoping review approach which aims to map the key concepts underpinning a research area especially where an area has not been reviewed comprehensively before (PRISMA-ScR).¹⁰

Our search strategy utilized subject heading searches: ‘Multiple Sclerosis’ and ‘wearable electronic devices’, as well as keywords ‘wearable technology’, and ‘electronic devices’. The literature search was conducted using MEDLINE (via PubMed) and Embase (via OVID) databases. This search included articles published from database inception to 30 May 2019. Additional searches looked at authors that have frequently published with different devices as well as forward and backward citation tracking of included papers. The scoping review followed the PRISMA-ScR guidelines.¹¹

When examining suitability of a wearable device for use in a UK wide multi-centre platform trial, we considered several factors: reproducibility (defined as the number of studies examining the solution in

MS), feasibility (including cost), patient adaptability and prior use in an RCT. The results of this is shown in Tables 2 and 3.

Study Eligibility Criteria

The inclusion criteria were defined as: (1) primary research studies that used wearable technology in a cohort of PwMS of all ages (adult or paediatric), (2) studies from any geographical location, (3) reported in the English language. Exclusion criteria were defined as: (1) wearable solutions intended for another health condition, (2) non-wearable solutions, (3) non-primary research such as narrative reviews, (4) abstracts that did not have full-text available.

After screening titles and abstracts, duplicates were removed and the full-text of each paper was assessed for eligibility according to the criteria stated above.

Data Extraction

The data to be extracted for each article were determined in consultation with the second author (GP) and a data extraction form was created. Descriptive characteristics were extracted where available for: (1) wearable device, (2) cohort, (3) type of study, (4) purpose, (5) functional area of assessment and (6) outcome.

Developers of the wearable technology were separated into the following categories:

- Health-care related agency: Hospitals, clinics, or government organisations directly related to health care
- Pharmaceutical company: entities with commercial purposes to research, develop, market or distribute drugs in the context of healthcare
- Educational organisation: any educational organisations such as universities, colleges, libraries or schools not directly related to health care
- Small and medium enterprises: start-ups, software developing companies, or any other private organization that identified themselves as an enterprise and not individuals

Results:

The searches yielded 1,880 potentially relevant articles. Removing duplicates and applying the eligibility criteria resulted in a total of 35 unique MS wearable technology solutions, which included 3 unique

solutions that were yielded from conferences and scientific meetings. Figure 1 describes the PRISMA flow diagram.

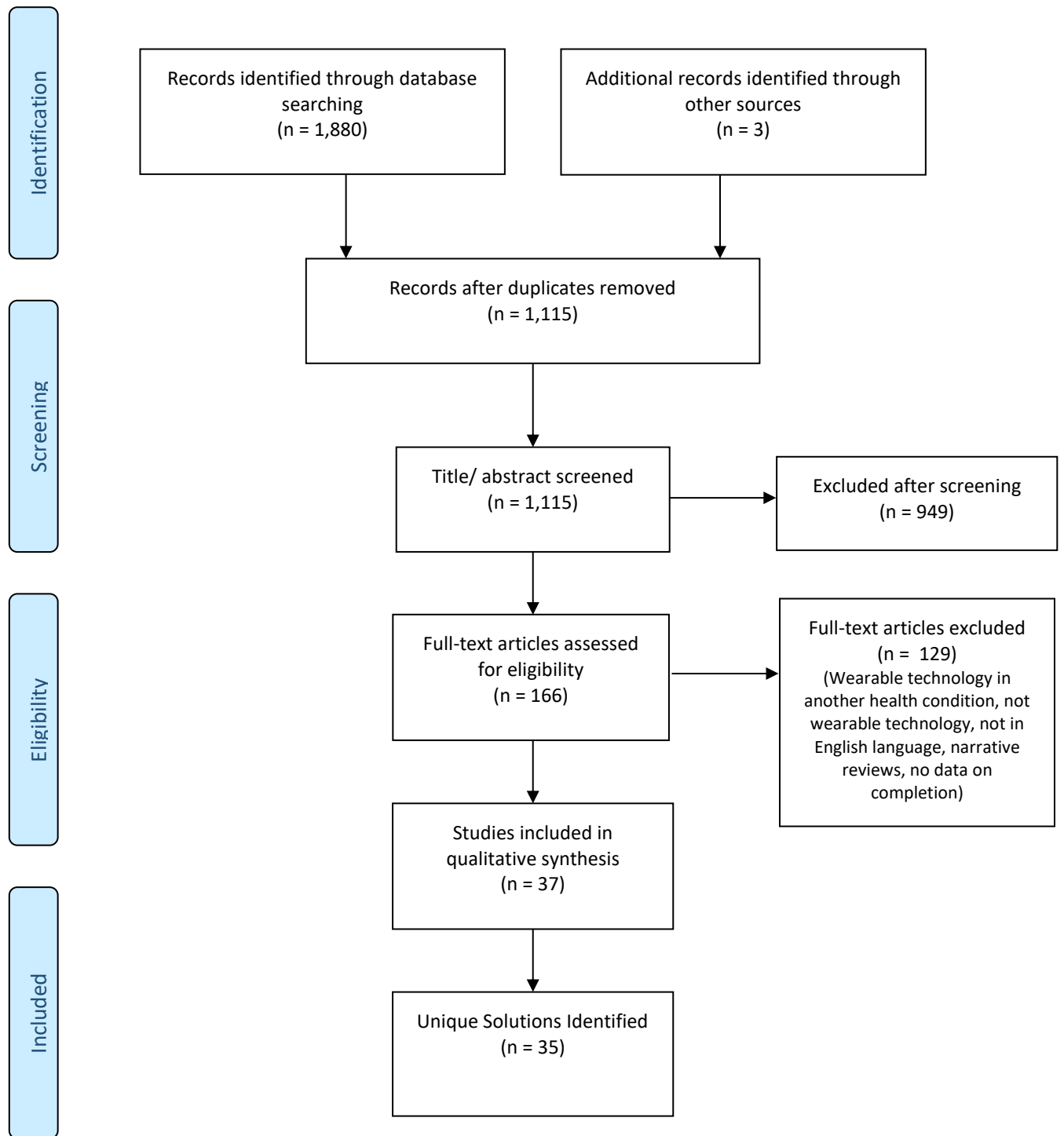


Figure 1. PRISMA Flow Diagram ¹²

The list of the included wearable technology solutions and the frequency with which they appeared in validated studies is shown in Table 2. A majority of the solutions that were used in studies in PwMS were applications (apps), accelerometers and activity monitors. The older studies predominantly focused on measuring activity, walking or gait since activity monitors, accelerometers and gyroscopes were the most readily available and advanced technology at the time. This result is not unexpected because the nature of MS disease progression would require sensors focused on assessments based on activity and function, both easily derived from accelerometers. Included are four unique app solutions for cognition, which were all created more recently, as apps are becoming an easier wearable technology to develop and deploy. There were a handful of wearables that focused on fatigue, mood, quality of life (QoL) and self-management. At the time of review, all wearables identified had only been used in observational or interventional studies.

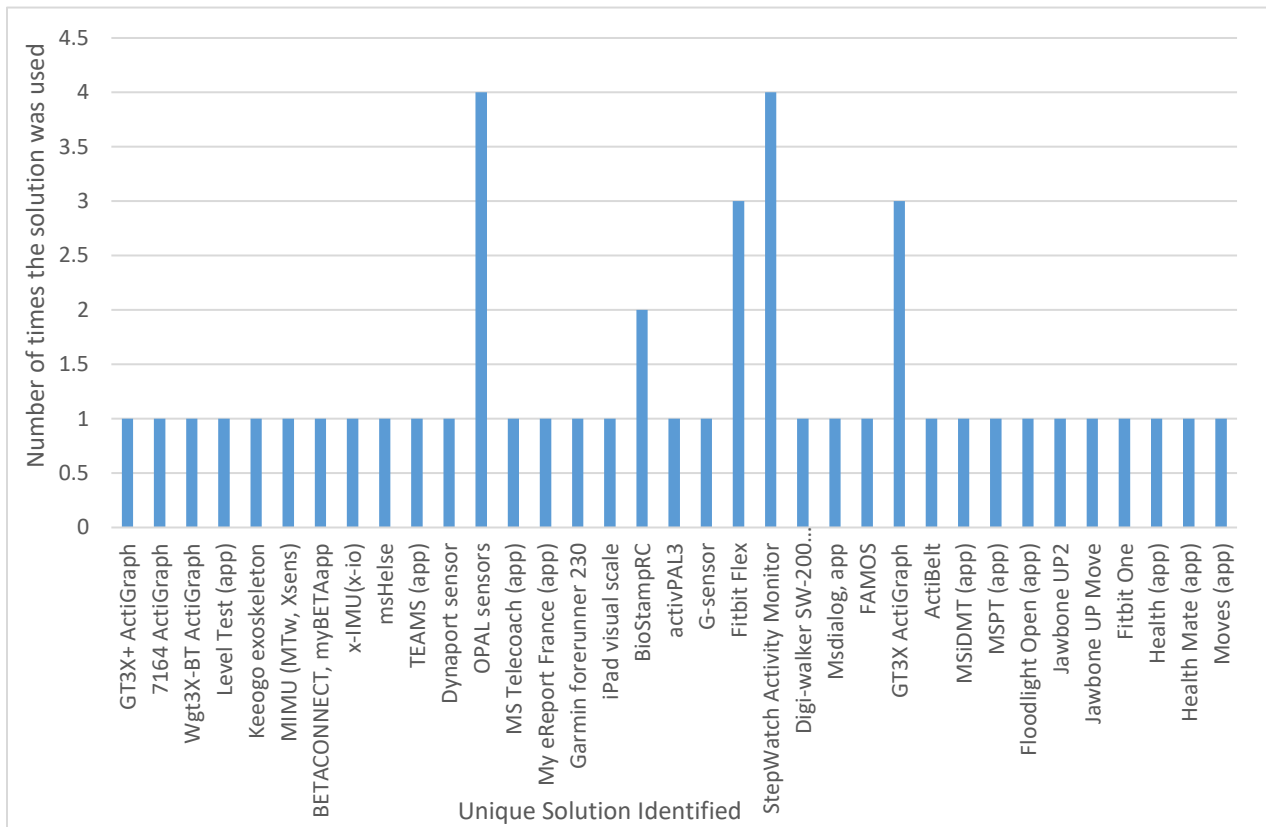


Table 2. Unique devices and prevalence of appearance

A summary of the general characteristics of the unique wearable technology solutions found are shown in Table 3 which can be found in the appendix.

There is significant variability in the per unit cost of each product and the decision as to which wearable to use depends largely on the study budget and outcomes of interest. Costs may vary significantly when using a physical wearable sensor compared to a smart-device application. Aside from per unit cost, other considerations include repair or replacement of faulty devices, annual maintenance charges, software package costs, return of devices, charging capabilities and collection of data (postage vs remote upload). Physical wearable sensors risk being 'phased out' and being replaced with newer models that have not been tested in an MS population. Applications may alleviate this problem by sending out software updates, which the user can download. Users could however face problems if this update exceeds the smart-device support capability.

There does seem to be a shift towards developing more validated wearable technology solutions for MS and focusing on health-care adoption to make sure that dissemination of the solutions is more successful and reaches a wider population. This is seen by the increase in the number of publications related to the subject of wearable technology in MS. Additionally, as a result of an increased number of solutions being validated, wearable technologies are now becoming more utilised in RCTs. At the time of writing this review, there are no published RCTs that utilises wearable technology, however we are aware of several other RCTs that are currently being run, that employ wearable technology such as the SPI2 and TEAMS studies.^{13,14}

Whilst doing this review, we identified 10 (27%) solutions that we classed as 'private' solutions as they had been created, tested, and not available to the public, as shown in table 3. This seems to have happened for various reasons including: not having the necessary resources to further validate or improve the solution or not having enough resources to gain regulatory approval. All of the identified solutions that are private and unavailable were created by health-care or educational organisations. Ideally, independent validation prior to clinical or research use seems appropriate however this may not be feasible due to on-going costs. When comparing this to the solutions created or funded by pharmaceutical companies, for example the FLOODLIGHT app and the MSPT, it was shown that 98% of the solutions created by pharmaceutical companies were successfully implemented and disseminated, as they had enough resources to manage the on-going cost and effort required to gain regulatory approval and market the products.

Limiting factors to consider when developing wearable technology is adherence. PwMS have shown a high level of acceptance when using smart-phone applications (apps), although this may wear off as the disease progresses due to handicaps (for example decreased hand dexterity).¹⁵ Factors to consider when designing a solution are: convenience, placement of the wearable device, appearance of the sensor, and feedback of results to the PwMS. Patient-feedback is extremely important in keeping PwMS interested and engaged in their own health. Many solutions have opted to patient-friendly readouts whilst more complex data and parameters are available to the respective clinicians and researchers.¹⁶

Another limiting factor, from a UK perspective, was the approach from regulatory bodies. Stricter guidelines determined what was seen as a medical device or classed as an observational tool. New guidelines which have recently come into effect, such as the new Evidence Standards Framework by NICE in March 2019 and the Regulation (EU) 2017/745 by the European Parliament (May 2020), will also work to create stricter guidance for patient safety, security monitoring and data security. Many solutions that are available elsewhere, have struggled to implement themselves outside of research in the United Kingdom due to these guidelines.

Limitations

Although we used a detailed process to search and document the currently validated solutions in MS, there were several limitations. The nature of this scoping report was web-search based and thus relied on university subscription to journals to access the papers, although only 5/1115 titles screened could not be accessed in this way. The inclusion of only English language papers may also be considered a limitation.

Conclusion

In the coming years, we can expect to see more sensitive and comprehensive measures being developed, with the idea of using wearable solutions perhaps as the gold standard to measure outcome measures in studies and clinical practice. However, at present, guidelines on what wearable technology should be used in clinical practice and research are absent and this is an area that will require considerable attention and stringency.

Whilst doing the review we came across many unvalidated solutions available for PwMS across a range of outcome measures, most of them being phone or iPad solutions. We classed a solution as 'unvalidated' if there was an inability to demonstrate test-retest reliability and/or failure to demonstrate difference

between healthy controls and PwMS. In comparison the validated solutions are rather limited, but are most advanced particularly in measurements of gait (characteristics) and balance. These solutions often provide the greatest accuracy and acceptance rate, as gait is one of the earliest outcome measures explored in MS wearable solutions.

Also with the advances in mobile technology, more solutions are focusing on utilising common wearables such as smart phones, smart watches, and tablets, to increase accessibility and minimise costs to the user. Looking forward, there is also a change occurring from single measure solutions to multi-measure and multi-sensor solutions, such as the Floodlight Open app, which utilises multiple sensors within a smart-phone to remotely measure gait, cognition and upper limb function.

As development in wearable technology in MS is still on-going, we can expect to see newer solutions focusing on other areas with technology advancements that allow for more upper body and cognitive measures. There is a dearth of validated solutions available for fatigue, mood, and pain.

The future of wearable technology in multiple sclerosis therefore looks promising with the potential to become a primary, co-primary or adjunctive monitoring tool in research and clinical practice.

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Appendix:

Table 3: Summary of unique solutions and their general characteristics

Wearable in Use	Cohort (n =)	Type of Study	Purpose	Functional area of assessment	Outcome
BETACONNECT, myBETAapp	> 100 MS	Interventional	Bayer produced app to assist the BETACONNECT auto injector and to help self-manage symptoms and dose.	Injection / Self-management	Shown to be an effective patient self-management tool for disease modifying therapy alongside auto injector.
FitBit Flex	95 MS	Interventional	To assess continuous step count activity remotely among PwMS for 1 year and determine how average daily step count is associated with other measures of MS disability.	Lower limb	Appears to be feasible to monitor for 1 year. It showed a decrease in average daily step count correlated to worsening of standard ambulatory measures.
Keeogo exoskeleton	29 MS	Interventional	An exoskeleton for lower-extremity to enable PwMS to benefit from exercise and physical activity.	Lower limb	Lower extremity exoskeleton, exercise-mediated benefit to PwMS that improves unassisted gait endurance and stair climbing.
TEAMS (private app)	10 MS	Observational	A Tailored tele rehabilitation app: Participant-Centered Development and Usability Study	Activity level	App that allows for PwMS to follow an exercise program and showed good usability. Currently being studied in an RCT.
StepWatch Activity Monitor	64 MS	Observational	Understanding walking activity in MS: step count, walking intensity and uninterrupted walking activity duration related to degree of disability.	Activity level	Results showed everyday walking in PwMS was not high and that PwMS rarely walk for more than six minutes uninterrupted.
Digi-walker SW-200 pedometer, Jawbone UP2, Jawbone UP Move, Fitbit Flex and Fitbit One AND Health app, Health Mate, Moves	45 MS	Observational	This study examined the accuracy and precision of common smartphone applications and motion sensors for measuring steps taken by MS patients while walking on a treadmill.	Activity level	Fitbit One was the best and most precise solutions for measuring steps but more research is needed before inclusion in clinical research.
StepWatch Activity Monitor, GT3X+ ActiGraph	63 MS	Observational	Accuracy of StepWatch and ActiGraph accelerometers for measuring steps taken among persons with multiple sclerosis.	Activity level	Results showed that the StepWatch was a more accurate choice of accelerometer, especially in those with higher disability levels.
7164 and GT3X ActiGraph	41 MS, 41 HC	Observational	Comparison of ActiGraph activity monitors in persons with multiple sclerosis and controls.	Activity level	There was enough discrepancy between the two models to show they are not interchangeable under free-living conditions.

StepWatch Step Activity Monitor (SAM)	9 MS	Observational	Validity of the StepWatch Step Activity Monitor: preliminary findings for use in persons with Parkinson disease and multiple sclerosis.	Activity level	Results showed that the StepWatch accurately measured step count for those with MS
ActiBelt	30 MS	Observational	Creating a robust and autonomous measurement device for long-term monitoring of patient activity	Activity level	Preliminary results are promising but the algorithm needs to be modified to allow for more sensitivity
Private app	22 MS, 17 HC	Observational	This study illustrated some of the novel approaches that smartphones provide to monitor MS patients in their natural setting	Activity level Cognition Fatigue	Results show the feasibility of and barriers to deploying a smartphone platform to gather passive and active data. Overall positive data and shows smartphone platform may therefore enable large-scale studies of PwMS.
MS TeleCoach (app)	75 MS	Observational	Assess feasibility of the MS TeleCoach offering tele monitoring of fatigue, telecoaching of physical activity and energy management over a 12-week period.	Activity level Fatigue	Intervention was well accepted and shows use of MS TeleCoach as a self-management tool in PwMS suffering from mild disability and moderate to severe fatigue appeared to be feasible.
activPAL3	20 MS	Observational	Validity of the activPAL3 activity monitor in people moderately affected by Multiple Sclerosis.	Activity level Lower limb	Good for moderately affected PwMS - slow walking cadence produced large inaccuracies
ActiGraph Wgt3X-BT	80 MS	Observational	Used to monitor activity levels in a trial to see effect of core exercise on PwMS	Activity level Lower limb	Core exercises helped PwMS increase activity levels
Fitbit Flex, GT3X ActiGraph	99 MS	Observational	Continuous daily assessment of multiple sclerosis disability using remote step count monitoring.	Activity level Lower limb	Evaluated in a RMS and PMS cohort and shown to support remote step count monitoring as an exploratory outcome in MS trials.
Phone app (private)	5 MS	Observational	Self-management phone app for PwMS to capture data about symptoms, physical activities, mood and goals.	Activity level Mood	Created a low fidelity prototype and the high fidelity prototype is being built to be further evaluated
Floodlight Open	76 MS, 25 HC	Observational	Testing feasibility of remote active testing and passive monitoring using smartphones over 24 weeks. These tests included Cognition (SDMT), Upper Limb (Pinching test and	Balance Cognition Lower limb Upper limb Quality of life	Floodlight Open showed strong correlations to the SDMT, 9HPT and 25FW. Older version of the app (FLOODLIGHT) also included the MSIS-29 which had a good correlation however this

			Draw a Shape), Gait and Posture (25FW, 5UTT), Daily mood questionnaires and symptom tracker.		module is unavailable for the FLOODLIGHT Open model.
MSPT	51 MS, 49 HC	Observational	The Multiple Sclerosis Performance Test: and iPad based disability assessment tool. Includes 5 performance modules: Walking speed to simulate walking speed test (WST), balance Test, Manual Dexterity Test for upper limb function, Processing Speed Test to simulate the SDMT, Low contrast letter acuity test designed to simulate the Sloan LCLA test.	Balance Cognition Lower limb Upper limb Visual	Well accepted by patients and strong correlations to their respective standard neurological test. Currently being tested for use in a clinical setting.
MSiDMT (private)	40 MS	Observational	iPad based SDMT test, testing correlation of the iPad solution to the SDMT	Cognition	There was a strong correlation between the MSiDMT and the SDMT and it was well accepted by PwMS.
Level Test (private app)	29 MS	Observational	Smart phone embedded sensors to measure various neurological functions using gamification.	Cognition	Measured outcomes showed moderate correlations with various clinical scales and components of neurological examination. Certain level tests discriminated MS from HC.
Activity monitor (private)	21 MS	Observational	Examine the impact of MS disability on physical activity behaviours involving ambulation.	Lower limb	The activity monitor showed that daily step strongly related to gait and balance measures. EDSS and MSWS scores also strongly related to daily step count.
MIMU (MTw, Xsens)	20 HC and 10 MS	Observational	Using sensors to try and detect gait characteristics whilst ascending stairs.	Lower limb	Detected MS specific gait patterns that would not be picked up otherwise
x-IMU(x-io)	17 MS, 23 HC	Observational	Quantifying mobility impairment in MS, with a thigh-derived inertial sensor metric to assess the sit-to stand and stand-to-sit transitions in the Timed Up and Go task.	Lower limb	Shown to be effective at differentiating between HC and MS
Dynaport sensor, OPAL sensors	14 MS	Observational	Using sensors to quantify gait characteristics and gait deficits from prolonged daily living measurements.	Lower limb	Validated a method to quantify walking in real life in PwMS.

OPAL sensors	12 MS, 12 HC	Observational	Using sensors, to quantify head and pelvis movement patterns that occur in PwMS with disability and determine how these secondary gait compensations impact on gait stability.	Lower limb	Efficient way to screen for excessive compensatory movements and provides information that impact mobility, stride time, gait stability. Good for identifying high risk of falls.
Garmin forerunner 230	73 MS	Observational	Evaluate the agreement between patients' and neurologists' estimates of maximum walking ability and patients' mean maximum walking ability measured in daily life using GPS smart watch.	Lower limb	Confirmed patient estimate of distance walked is poor and shows that remote monitoring is a good way forward.
BioStampRC	30 MS	Observational	A machine learning approach for gait speed estimation using skin-mounted wearable sensors.	Lower limb	Results support the use of wearable accelerometer arrays for estimating walking speed in normal subjects and their extension to MS patient cohorts with gait impairment.
OPAL sensors	52 MS, 21 HC	Observational	Validation study of the Instrumented Push and Release Test to quantify postural responses in persons with MS.	Lower limb	Demonstrated strong agreement and correlation between sensor based metrics and gold standard lab measurements. Several metrics were shown to be different between PwMS and HC.
BioStampRC, GT3X ActiGraph	45 MS, 15 HC	Observational	Monitoring gait in multiple sclerosis with novel wearable motion sensors.	Lower limb	Results showed that the BioStamp most accurate device
G-sensor	105 MS, 47 HC	Observational	This study aims to verify the feasibility of using wearable accelerometers in an ambulatory environment to assess spatiotemporal parameters of gait in people with Multiple Sclerosis (PwMS), as well as the correlation of objective data with patient-reported outcomes.	Lower limb	Wearable accelerometers are a useful tool for assessing gait performance in PwMS in a clinical setting, especially in mild to moderate disability.
OPAL sensors	5 MS, 13 HC	Observational	To determine whether gyroscopic corrections improve wearable sensor data prior to measuring dynamic sway in the gait of people with Multiple Sclerosis.	Lower limb	The visualisation of asymmetric pelvic sway in people with MS illustrates the potential to better understand their mobility impairments for reducing fall risk.

My eReport France (private app)	180 MS	Observational	Mobile phone application for drug adverse reaction reporting by patients with RRMS in a randomised controlled trial.	Self-management	Study not completed and results not yet available
Msdialog, app	76 MS	Observational	A web- and mobile-based software application, captures data on self-administration of subcutaneous interferon β -1a, clinical outcomes, and patient-reported outcomes in patients with multiple sclerosis outside the clinic	Self-management	Well accepted by users and user retention was high over 6 weeks. PwMS found it easy to use and superior to previous methods for tracking health.
FAMOS (private)	17 MS, 9 HC	Observational	A wireless body measurement system to study fatigue in multiple sclerosis.	Fatigue	Preliminary results show significant differences between fatigued PwMS and healthy controls. This provides a new approach to study fatigue in MS but needs to be validated through larger clinical trials.
iPad visual scale (private)	52 MS, 52 HC	Observational	To explore the reliability and feasibility of electronic visual analogue scales in PwMS and health individuals	Fatigue Quality of life	Reliable and useful for PwMS to register fatigue, pain, anxiety and QOL
Phone app (private)	76 MS, 19 HC	Observational	Two smartphone tests of fine finger movements to see if correlated with neurological examination.	Upper limb	Good correlation with 9HPT and captured richer data than traditional measures

Legend

MS: Multiple Sclerosis, HC: Healthy Control, RMS: Relapsing Multiple Sclerosis, RRMS: relapsing Remitting Multiple Sclerosis, PMS: Progressive Multiple Sclerosis, PwMS: People with multiple sclerosis , RCT: Randomised controlled trial, SDMT: Single Digit Modality Test, 25FW: 25 Foot Walk, 5UTT: 5 U-Turn Test, MSIS-29: Multiple Sclerosis Impact Scale, WST: Walking Speed Test, MSWS: Multiple Sclerosis Walking Scale, QoL: Quality of Life , 9HPT: 9-Hole Peg Test, Sloan LCLA: Sloan Low Contrast Letter Acuity , GPS: Global Positioning System