The Benefits of a United Kingdom Multiple Sclerosis Register

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Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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Abstract

Background
In rare diseases such as multiple sclerosis (MS) the capture of data purely from clinical trials or hospital cohorts is insufficient for fully understanding the multifaceted impacts of the disease. MS is the most common non-traumatic cause of disability in young adults worldwide. The disease is multifactorial, profoundly impacts quality of life, and life span is affected by 7 to 14 years. Diagnosis has become easier and newer treatment options have proliferated but monitoring and researching the disease's various impacts remains challenging with a largely clinical focus on ‘hard outcomes’ such as imaging, biomarkers and in-person clinically assessed scales.

Disease registers are best positioned to capture data about chronic disease such as MS as they allow for longitudinal capture from a variety of sources, including clinical outcomes but also data from patients/participants. Moving disease registers away from paper-based capture has allowed for easier, more accurate and rapid capture from these sources but can also add new data sources such as novel outcome measures, data from other devices and then facilitate linkage of that data across all these domains.

Aim
To communicate the learning and experiences from building a UK-wide register which captures multifaceted MS data, in order to inform the development of similar registers for other conditions.

Methods
Construction of an electronic platform sufficiently flexible to capture data from people with MS in the form of patient/participant reported outcomes, from the NHS as clinical datasets, and the technology to link these datasets together in a privacy protecting way to make these datasets available to other researchers. The data capture technology must be robust enough to add additional sources or datasets as needed whilst maintaining the core elements of reproducible research.

Results
A robust, flexible, privacy-protecting secure research-ready disease register was constructed containing data directly captured from more than 20,000 participants, 50 NHS sites with more than 1 million completed Patient Reported Outcomes (PRO), clinically transmitted datasets and other diverse outcomes collected. Pseudonymised elements of that data, subject to robust governance and review, are released to appropriately qualified researchers to carry out their own research on the platform.

A number of important lessons were learned in the construction of this research register. The most important being that involvement of people affected by the disease in all aspects of the project is crucial for enabling key aspects of a functional register, including the collection of varied and complementary data, the levels of engagement required for longitudinal research, and assisting with the direction of research. Feedback loops in this participant-register relationship create a more holistic research instrument.

Another vital aspect is the ability to carry out data linkage both within the project and to outside routinely collected datasets, expanding the scope of potential research without adding burden to participants.

Flexibility of approach is particularly important for chronic disease where aetiology is uncertain and impact of lifestyle elements on the disease and the person are evolving.

Maintaining these core principles of participant engagement, flexibility, and the ability to include novel datasets allows the collection of real-world data from individuals, their clinicians, and other relevant sources and stakeholders, leading to diverse and significant research into the disease.

Conclusion
The UK MS Register can serve as a model for the design and construction of disease registers, capturing validated data from diverse data sources with reference to patients' requirements and desires and satisfying researchers and clinicians needs for an unbiased, varied research ready dataset.

Precis

The work in this thesis describes my creation of a novel disease register, using multiple sclerosis as its exemplar. This thesis will cover eight papers that chart the stages of development, initial data collection, validation, and expansion of the MS Register.

Along with the creation of the Register these publications will show my evolution as a researcher and data scientist as these strands are brought together in the development of an essential piece of infrastructure that is now used by MS researchers across the world.

The United Kingdom Multiple Sclerosis Register (UKMSR) as a platform has been a synergistic development of participant engagement, information architecture construction, stakeholder involvement combined with a fundamental research underpinning that brings these elements together. For the reader it may be conceptually helpful to view the 'MS Register' as a product that has been introduced with a lifecycle approach. Figure 1 shows a conceptual map of this thesis:

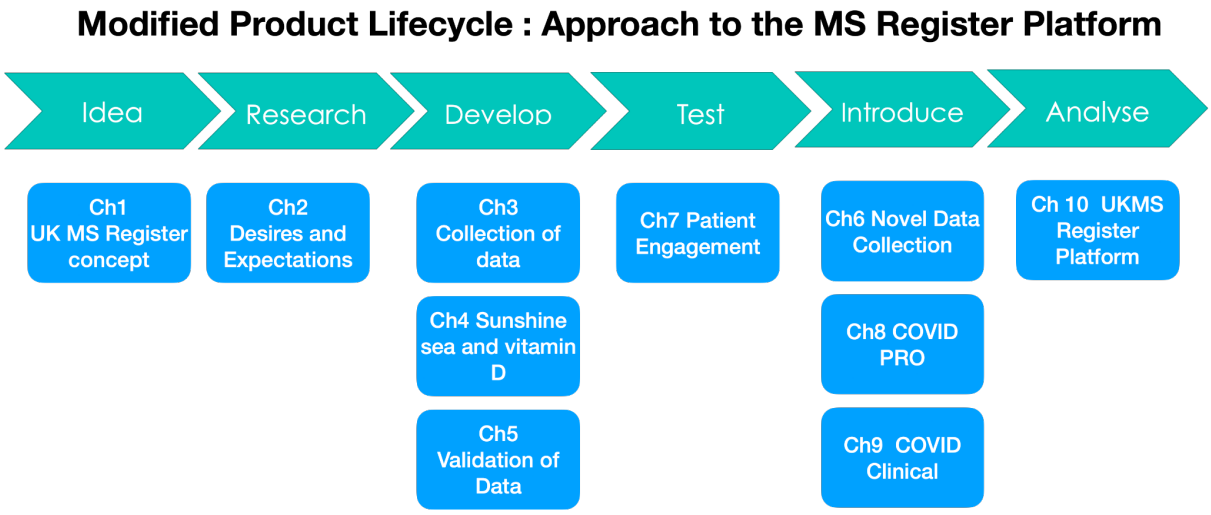

Figure 1: Product lifecycle approach to the MS Register

Chapter 1 gives an introduction to the reasons for the creation of a multiple sclerosis register, the drivers behind its data sources, and an overview of MS. It also explores what makes the creation of a register distinct from the collection of trial data or routine clinical data. The path to the current iteration of the MS Register is then set out using a number of peer-reviewed papers.

Chapter 2, "Desirability and expectations of the UK MS Register: views of people with MS", sets out what people with MS expected to get from a nominal 'MS Register'. This was a qualitative research project to gauge what people with MS expected of a 'web-based' platform in order to elicit their expectations and hopes for an MS Register. Focus groups and concept analysis were used as part of this study.

Chapter 3, "The feasibility of collecting information from people with multiple sclerosis for the UK MS Register via a web portal: characterising a cohort of people with MS", describes the first paper produced following the public launch of the MS Register platform. This sets out the types of Patient Reported Outcomes (PROs) that were captured as part of the initial Register, the schedule that they would be collected on and the value that they had in showing disease-related impact via the PRO data. It also demonstrates that there was a cohort of people with MS who would willingly participate in the submission of electronic data for MS research.

Chapter 4, "Sunshine, sea and season of birth: MS incidence in Wales", brings the data linkage possibilities of the MS Register to the fore, in this case demonstrating linked data within the Secure Anonymised Information Linkage (SAIL) databank. This allowed for the development of an initial case-finding algorithm that could identify multiple sclerosis patients within routinely collected data. The study found that the incidence of MS in Wales at the time was similar to data published in Scotland, and that environmental factors may have a similar influence to those reported in other national datasets.

Chapter 5, "Validating the portal population of the UK MS Register", continues the illustration of the utility of linked data by connecting participant PROs with clinical data from

NHS Sites. This was a defining concept of the platform – the ability to link datasets from multiple sources as part of a longitudinal study and, while doing so, validate the online population as having a neurologist-confirmed diagnosis of MS.

In **Chapter 6,** "**A rapid electronic cognitive assessment measure for multiple sclerosis: validation of Cognitive Reaction, an electronic version of the Symbol Digit Modalities Test",** the ability of the platform to enable the capture of novel and diverse datasets and then link to the Register is highlighted, as a tablet-based application to carry out a cognitive assessment is developed and deployed. This shows that the platform could expand to encompass data from new sources and new outcome measures dynamically, and that data would have wider utility; both within the Register platform and when extended to other research studies.

Chapter 7, "Can we improve the monitoring of people with multiple sclerosis using simple tools, data sharing, and patient engagement?", revisits the concepts set out in Chapter 2, ensuring that people with the disease are at the heart of new research developments and that their input can shape and improve research and the platform with which they are working. This ensured that the concepts outlined in Chapter 2 had been implemented, and also that the platform could provide what people with MS expected to get out of the Register going forward; namely, that they could see visualisations of their own data should they choose to, and provide this to their clinicians.

In **Chapter 8, "COVID-19 is associated with new symptoms of multiple sclerosis that are prevented by disease modifying therapies",** I demonstrate the ability of the platform to respond rapidly by collecting valuable data from the outset of the COVID-19 pandemic. The MS Register deployed a questionnaire to people with MS even before the national lockdown began in the UK. This questionnaire, in context with the pre-existing PROs that were being collected, allowed the Register to capture data and publish extensively. This first paper, in collaboration with MS researchers from the University of Nottingham, discovered that patients on Disease Modifying Therapies (DMTs) had fewer symptoms than those not on DMT, and that this held true even in the light of a COVID-19 infection. This paper demonstrates the agility of the platform and its strong potential for collaboration.

Chapter 9, "COVID-19 in multiple sclerosis: clinically reported outcomes from the UK Multiple Sclerosis Register", continues the COVID-19 research but turns to the clinical data received by the MS Register during the pandemic. In this study, an electronic case return form that captured data around COVID-19 infection, MS type, disease severity, and comorbidities was deployed across the UK. It was found that increasing age and male gender were the most significant factors for a poor outcome and that the second wave had overall better outcomes than the first wave.

In **Chapter 10 "Discussion",** the papers in this thesis are used to illustrate the current status of the MS Register platform and how it has had an impact on MS research in the UK. Lessons learned are highlighted, as is the way that the platform has enabled multiple other research projects to be carried out. Finally, the limitations and future directions for the Register are presented.

The work in this thesis illustrates, through publication, the development and evolution of an

electronic disease register. The value of longitudinal real-world data collection and the utility of a common research platform for people with MS, researchers in the field and for clinicians in practice, are demonstrated.

Publications related to this thesis

Osborne LA, Middleton RM, Jones KH, *et al.* **Desirability and Expectations of the UK MS Register: Views of People with MS**. *International Journal of Medical Informatics*. 2013;82:1104–10.

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outcomes from the UK Multiple Sclerosis Register. Multiple Sclerosis and Related Disorders 56, 103317. https://doi.org/10.1016/j.msard.2021.103317

Chapter 1: Introduction

Background

Multiple sclerosis and the need for long-term data collection

Multiple Sclerosis (MS) is the most common non traumatic disabling disease that affects young adults worldwide ((Filippi et al., 2018), (Brownlee et al., 2017)). The disease is thought to affect more than 126,000 (Mackenzie et al., 2014) people in the UK and they can experience high levels of disability and impaired quality of life. The disease can affect life expectancy in the range of 7 to 14 years (Scalfari et al., 2013), with most people with MS (pwMS) still being alive more than 25 years after clinical onset (Leray et al., 2016). This prolonged period of increasing disability MS is noted for has led to the development of a large number of potential treatments for the disease that have become available over the last 20 years (McGinley et al., 2021), although these come with their own attendant risks.

The disease is diagnosed in women three times as often as men (Hirst et al., 2008) and is known for its effect on the central nervous system. It has a variable disease course and can present with changes in balance, cognition, mobility, and vision, which can all be affected in varying amounts over the duration of the disease. Although the effective diagnosis of the disease has improved (Brownlee et al., 2017) the causes of MS have still to be categorically defined, while it is almost certain that the interaction between Epstein-Barr Virus (EBV) and a patient's genome is a major factor (Bjornevik et al., 2022). It is therefore important that other variables must be accounted for as part of the work to establish causality, especially relevant here are the impacts of Vitamin D (Sintzel et al., 2018), diet (Evans et al., 2019), deprivation (Harding et al., 2019) and other environmental or lifestyle factors (Belbasis et al., 2015).

A diagnosis of MS is made based on clinical symptoms and signs. Presentation of the disease is most typical with an acute unilateral optic neuritis, asymmetric limb weakness or L'hermitte’s sign (Brownlee et al., 2017). The evolution of the diagnostic criteria has been in lockstep with the technology of the time, so evolving from symptoms and clinical tests only (Schumacher et al., 1965) in the 1960s, to Cerebrospinal fluid (CSF) tests confirmed by laboratory in the 1980s (Poser et al., 1983) to confirmation by Magnetic Resonance Imaging (MRI) in early 2000 (McDonald et al., 2001) and a revision to these criteria in 2005 and 2010 (Polman et al., 2011). Currently the clinical symptoms require the dissemination in time and space of two lesions on MRI (Filippi et al., 2016) which are a more finely tuned version of the McDonald criteria from 2000.

The disease has a number of subtypes, and the majority of people (80-95%), (Filippi et al., 2018), (Brownlee et al., 2017)) are diagnosed with Relapsing Remitting MS (RRMS). This form of the disease is characterised by having distinct 'relapses' or attacks where function is lost but can be regained over the course of a month or so. Over time, typically more than 10 to 15 years, the disability from these relapses increases and the patient becomes progressive. Secondary Progressive MS follows RRMS, observable relapses stop, and progression becomes dominant. Primary Progressive MS (PPMS) occurs in 5-15% of cases (Miller and Leary, 2007) where progression is more or less continuous from onset.

The majority of current disease treatments for MS are focussed on RRMS patients, with disease modifying therapies (DMT) for progressive MS becoming available from 2017 (Montalban et al., 2017) and then only for younger less disabled patients. Certainly this is the case within the UK ("Products - Multiple sclerosis | Topic | NICE," 2022), although treatment parameters vary across Europe and the rest of the world.

These uncertainties about cause, diagnosis, treatment, living with the disease and how that impacts all aspects of the activities of daily living make the collection of a broad range of disease-specific data essential. Having a robust longitudinal repository of data for and about people with MS in the UK would form an essential element of scientific research infrastructure for the study of multiple sclerosis, the creation of a United Kingdom Multiple Sclerosis Register (UKMSR) would enable this.

Data collection and evidence-based medicine

Research on 'health data' is typically broken into two main areas:

1. Clinical Trials, with Randomised Controlled Trials (RCTs) being the gold standard.
2. Observational studies, which encompass Electronic Health Record (EHR) data, routine data collections, and other studies where patients are not randomised into a control group.

"*Observational studies observe differences in outcomes after treatment decisions have been made* " (Hannan, 2008). For treating clinicians there is an inclination that clinical trials are the standard by which all other research and datasets must be judged. This is entirely understandable as decisions to give patients a particular treatment should be based only on data with the greatest amount of rigour, and even more so if multiple randomised clinical trials support that conclusion. The 'evidence pyramid' (Figure 2) supports this traditional hierarchy of separation of RCTs with observational studies ((Straus et al., 2018),(Murad et al., 2016)) being everything below the RCT line.

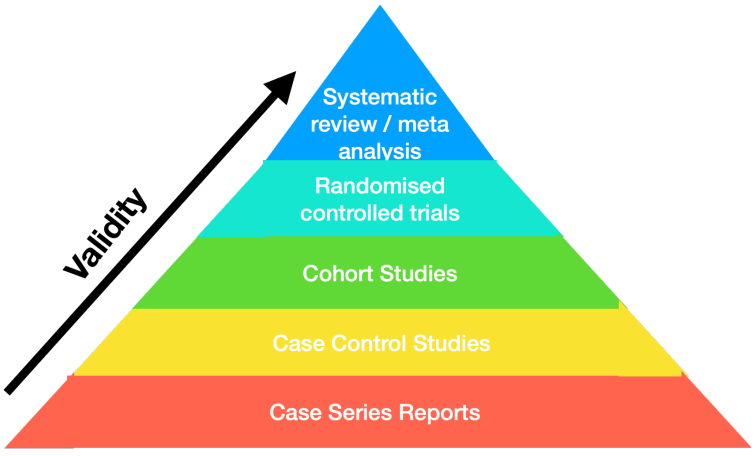

Figure 2 : The Evidence Pyramid

This does not mean that data contained within observational studies should be disregarded, more that they are constantly striving to attain a level of validity close enough to RCT's that their research carries similar weight. In computer science there is the maxim of *garbage in,*

garbage out, Charles Babbage himself, creator of the first programmable 'calculating engine' observed "*On two occasions I have been asked, "Pray, Mr. Babbage, if you put into the machine wrong figures, will the right answers come out?"* (Babbage, 2011). This gets to the heart of many of the issues with data collected outside clinical trials. Is it trustworthy? Has it been validated? Was the data collected according to research ethics? What is the data provenance? Has it been altered within the database and was a log kept? What are its biases? All of these questions and more are levelled at all studies, but they are generally more explicitly recorded and stated in RCTs.

To address some of these deficiencies there have been two significant initiatives to improve the reporting of data captured outside of clinical trials. The first of these, Strengthening the Reporting of Studies in Epidemiology (STROBE) (Vandenbroucke et al., 2007), is a checklist designed to highlight items that should be addressed as part of the descriptive reporting recommendations for observational studies. The intention of STROBE is to improve the transparency of *reporting* of studies not to ensure the study itself was well done. This uniformity in setting the language of how observational studies are presented to journals provides a more consistent approach and applies rigour to reporting.

The REporting of studies Conducted using Observational Routinely collected Data (RECORD) is an expansion of the STROBE checklist (Benchimol et al., 2015). RECORD takes the tenets of STROBE and extends it with additional reporting requirements for routine data sources to help improve the transparency and rigour of those types of study. By themselves STROBE and RECORD do not improve the quality of observational studies but by improving all elements of studies from design, data capture, validation, application of coding nomenclatures, methodologies applied and ultimately reporting on them then a higher quality standard will become evident.

Data in MS, as with other areas of medical research, spans the evidence pyramid; there are RCTs, cohort studies and routine data collections from healthcare providers. Again, it is rare that any of this data is truly 'long-term' or consistently captured. Clinical trials generally have a finite length of 'n' years with well-defined (if limited) outcome measures. Healthcare service data collection is long-term, but is focussed towards diagnosis and treatment and the storage and type of these data can vary widely by institution. Additionally, this data is rarely made accessible to other researchers due to data governance, ethical or commercial factors. The limitations of data collected for these purposes make longer term studies looking at mortality, long-term treatment efficacy, prodrome or burden of comorbidity extremely difficult to assess ((James et al., 2015), (Scalfari et al., 2013)). Registers in some sense can be thought of as being able to encompass many of the elements of the evidence pyramid, though they take dedicated design to become so.

Disease registers: a solution in MS

The establishment of registers for the collection of research data is not a new one; in order to gain knowledge about a disease or an intervention appropriate data must be collected to monitor the extent of the disease or the impact of the intervention. A "*registry" refers to both programs that collect and store data and the records that are so created*" (Gliklich et al., 2014). Patient registers have been harder to define, with the earliest comprehensive example being cited by (Brooke and Organization, 1974) as "a *file of documents containing*

uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose." These quotes get to the crux of registers. They are purposeful, systematic collections of data for a well-defined reason.

Disease registers are made up of primarily observational data, that is data that is generated as part of a patient's normal care or progress through interactions across the healthcare and research spectrum.

In 2010 the UK MS Society put out a tender, seeking a university or NHS organisation within the UK to build a multiple sclerosis register that would attempt to answer three requirements, namely:

1. To provide more accurate estimates of the number of people living with MS in the UK.
    a. To provide information from those on the Register of the economic and social impact of living with MS.
2. To clearly demonstrate the impact of a UK MS Register on the lives of PwMS.
3. To provide information and data to, and interface effectively with, MS Society national, regional, and local structures.

From the outset it was made clear that point two would be difficult to achieve but points one and three would be attainable. A traditional register within the MS research sphere at this point almost exclusively consisted of clinical data. The registers that were becoming established in the world were growing due to two primary factors. The first was the increasing accuracy of an MS Diagnosis following the introduction of the (McDonald et al., 2001) criteria; the second was the increase in first generation DMTs, with the requirement that their long-term outcomes were monitored (primarily with disability scoring at clinical visit). Examples of this type of Register were appearing in Sweden (Hillert and Stawiarz, 2015), Germany, (Flachenecker et al., 2005) and Denmark (Koch-Henriksen, 1999). There was also the introduction of a more global approach to the capture of MS clinical data in the MSBase Register (Butzkueven, n.d.) which launched in 2004. There was one other national MS register that was attempting to capture data directly from people with MS, rather than from clinicians: the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry in the United States (Marrie et al., 2007). The novel approach that the UK would take to answer the MS Society's questions was to capture data clinically *and* from pwMS.

A linked disease register

There are a large number of advantages to having the ability to link between data sources in a disease register. For example, linking between participant responses and clinical data allows for straightforward analysis of many aspects of the disease, e.g., are people with the disease reliable narrators of their condition? There is a lot more to be considered here, however. Reliance on clinical or trial records alone leads to gaps in the natural history of the disease and a large portion of time is spent by clinicians establishing what has happened to patients when they are outside of the clinic. How has the disease progressed? Are they on new medications? Have they developed new comorbidity? Has their social or carer situation changed?

The ability to deploy validated, reliable outcome metrics mean that many of these aspects

can be monitored while the patient is not in front of the clinician. This is important for researchers to better understand the impacts of the disease, assess areas such as quality of life, costs and can be useful to clinicians to make better judgments about disease progression. They can also be important for people with the disease to evaluate what is changing. There are multiple examples of the clinical effectiveness of Patient Reported Outcomes (PROs) (Revicki et al., 2008), assessment of cost (Goodwin et al., 2018) and the efficacy of self management. (Nolte et al., 2007)

There is also the aspect of being able to evaluate measures that otherwise would be impossible using just standard outcome measures such as disability scores. Aspects such as the impact of educational attainment on access to treatment, or the effects of increasing disability on employment and employability, may be incorporated. Lifestyle choices such as diet and smoking and their long-term effect on elements such as fatigue are made more difficult without having linkage in a disease register. As clinical trials are limited in time, the ability to look at all aspects of the disease for periods of time measured in decades allows for objective examination in the longer term.

Add to this the ability to link to novel datasets (such as cognitive measures) and ‘routine’ datasets (such as Hospital Episode Statistics (HES) or General Practice (GP) data) and the value increases exponentially. Prescribing data can be contextualised by anxiety and depression scores, and indices of multiple deprivation can be linked with education, diet and activity, all in the context of disease impact. Laboratory data for EBV infection can be linked with sequential Expanded Disability Status Scale (EDSS) scores later in life.

The research impacts of connecting these kinds of data become increasingly significant and grow further as ‘new’ data is added, for example an MRI or genetic dataset. These too can be linked to, allowing the correlation of self-reported relapse with MRI activity and hospital attendance. The outcome of connecting disparate and varied datasets over time allows for an ever-richer trove of data that has immense value for all stakeholders in the disease.

Methods

The UK MS Register was a new initiative to capture data from multiple sources, specifically:

1. Directly from people with MS
2. Clinical data from participating NHS treatment centres following informed consent
3. Routine healthcare repositories, such as the SAIL databank.

Where possible, records from (1), (2) and (3) would all be linked to form a densely populated longitudinal record of a person's experience of living with MS in the UK. Figure 3 illustrates the conceptual data model for the UKMSR.

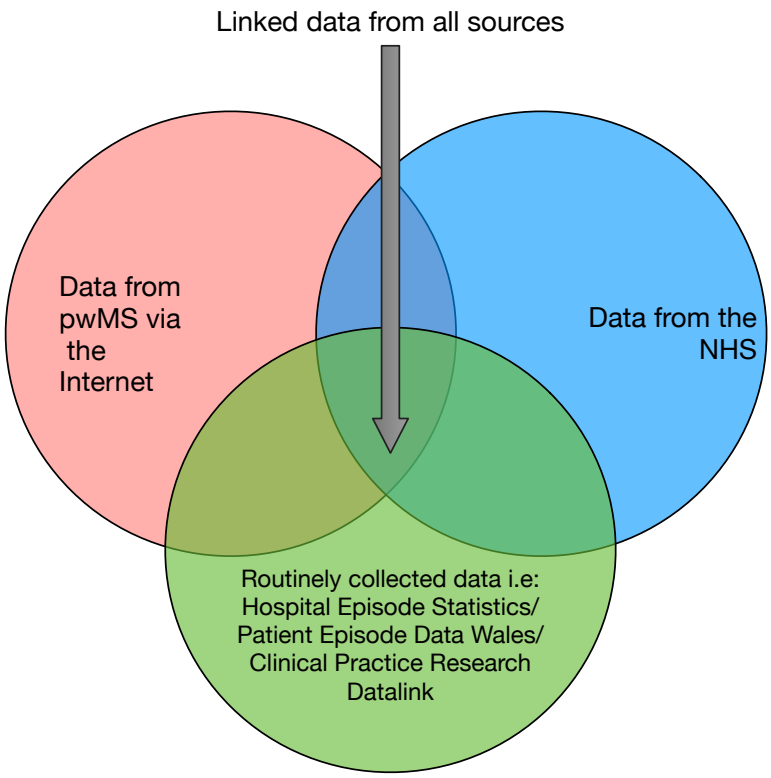

Figure 3 : The UK MS Register Conceptual Model

The three sources of data would be themselves be composed of multiple subsets:

- Data from people with MS would comprise multiple patient reported outcome measures – most of which would be standardised research instruments that would be asked longitudinally. Although the composition of these would be determined in discussion with pwMS, they would typically contain elements such as quality of life scores, impact of disease and impact of comorbidity. Other elements would also be captured, such as demographics, and epidemiological data.
- Data from the NHS in this instance was data directly captured from MS treatment centres - that is, routine care data from clinical teams directly looking after people with MS at their hospitals (using informed consent). Including treatment information, disease progression, demographics and epidemiology.
- Routinely collected data are those systematic collections of data that are captured as matter of course within healthcare systems. These are most normally captured by patient administration systems (PAS) as part of the operation of a hospital for example. Patient admitted to ward one, for exacerbation of chronic obstructive airways disease. Hospitalised for five days (known as a ‘spell’ in routine data) and discharged home. These data are typically for billing or modelling/understanding patient demand on a healthcare provider (see ‘Datasets and data capture’ below for more detail). These types of data are also captured by GPs and other providers. Examples of nationwide databanks of these data are available within England, as the Hospital Episode Statistics (HES) dataset and within Wales as the SAIL databank. HES was not an explicit linkage target at the outset of the Register project. Following appropriate governance, these datasets can be linked against using the data captured from research studies such as the MS Register – though they have immense value to researchers on their own. The unbiased capture of disease and

patient activity spanning multiple decades is hugely powerful. The addition of highly specific research data from a register only enhances this.

All these datasets were intended to be longitudinal, dynamic rather than static, and adaptable to new requirements and opportunities; that is, able to quickly add new patient reported outcome data to the patient facing portal and add new capture elements to the NHS data (such as annual review letters), or link to additional routinely collected data items such as pathology data.

Although the initiative would be supported by marketing from the MS Society, the implementation of this model was entirely left to the research team within health data science (then the Health Informatics Research Unit - HIRU) at Swansea University Medical School; the most important aspects of this implementation are covered below.

Parallel to the infrastructure requirements, it was essential to obtain approval from the NHS Health Research Ethics Service in order to ensure that the research being undertaken protected the dignity, rights and welfare of participants and was fit for purpose to be carried out in the NHS.

Ethics

The UK MS Register was granted research ethics approval by the National Research Ethics Service Committee (REC) - South West Central Bristol on the 9th of August 2011 as 11/SW/0160. This approval has subsequently been renewed at required intervals throughout the project, as 16/SW/0194 and most recently 21/SW/0085, by the same REC. All participants of the UK MS Register population must be aged at least 18 at the point they give informed consent at an NHS site or sign up to the web portal and have a confirmed diagnosis of multiple sclerosis from a UK neurologist.

Approach

The most fundamental design decision for the UKMSR would be that people with MS were to be involved in almost every part of the implementation process. This would include consultation on design and questionnaire choice, but also areas of development where their involvement may not have been such an obvious choice; therefore, pwMS were also part of the groups that developed the clinician- and researcher-focussed elements of the Register, alongside those with subject-specific professional expertise and other relevant stakeholders.

An electronic register

Given the amount of data that would likely need to be collected from various sources and the costs involved in capturing questionnaire data at scale on paper, there was an intention that the Register be as ‘paper free’ as possible. This was certainly the expectation for NHS sites as most MS data was already being captured electronically, meaning they would need only to provide data from existing datasets, rather than completing a traditional case return form.

An electronic register meant that people with MS would visit an online ‘portal’ to supply their PRO data. Research was planned to ensure that the patient-facing element would be acceptable to people with MS and designed so as to serve the purposes that the community

had in mind for an MS Register – beyond the requirement set out by the MS Society. That research forms Chapter 2 of this thesis.

Datasets and data capture

This process of choosing what data was to be captured was carried out in collaboration with pwMS, researchers and clinicians. We also paid close attention to what other international MS Registers were collecting (Flachenecker and Stuke, 2008) and carried out focus groups and research looking at outcome measures in use (Noble et al., 2012).The final draft was approved by the MS Register management committee prior to going live in 2011. All data, both clinical and participant facing would be captured to this specified dataset.

The design of the dataset variables needed to strike a balance between achieving the highest data quality possible, whilst maintaining a degree of flexibility to ensure maximum engagement from clinical sites, which have limited resources in terms of contributing data, as well as potentially missing data. With this in mind, mandatory fields were selected on the basis of highest research value. Validation was applied wherever possible with designated field formatting (for example, date fields must contain dates, and these dates must be between certain realistic ranges, or the user will receive an error).

For the process of validating the data captured we made a number of choices. Dates, for example, would be captured as per database standards, so a date formatted by an end user as DD/MM/YYYY would be stored in databases as YYYY-MM-DD. Where possible capture of data items would be to NHS specifications, for example there is a well-accepted data specification of ethnicity ("Ethnicity," n.d.) supplied by NHS digital. These options are the only ones that would be presented as items of data entry to participants or any data items captured from the NHS. Additionally, other data items (such as MS type, smoking status, household status) would be easily transferable to other coding nomenclatures where possible. A key area of sensitivity on the participant-facing aspect of the UKMSR was the matter of mandatory fields. MS is a disease that affects cognition as well as physical function. The earliest versions of the Register portal had fewer mandatory fields as we wanted to be sensitive to people being unable to remember exact dates of particular interactions with medical staff. Later iterations of the Register allowed for more 'fuzziness' in some of these data collection choices. For example, a date indicating progression to SPMS became just a year field rather than an exact DD/MM/YYYY.

Ideally the UKMSR would capture natively in a coding format such as the Systematised Nomenclature of Medicine - Clinical Terms (SNOMED-CT). The use of coding nomenclatures is standard practice in routine collections of healthcare data, stemming back hundreds of years at this point (Graunt, 1899). At the time the MS register was in development, more widespread acceptance of SNOMED was being implemented, the NHS was however still largely using the International Classification of Diseases Version 10 (ICD-10) (WHO, 2010) . Though powerful, well understood and accepted ICD lacked some definition compared to SNOMED. For example, the only code for MS in ICD-10 is G35 - '*Multiple Sclerosis'*. This lacks the granularity of SNOMED where the types of MS can be categorised correctly whilst still maintaining the ability to translate between nomenclatures. The SNOMED concept 24700007 (Multiple Sclerosis (disorder)) directly translates to G35 in ICD-10, however in SNOMED we also have the facility to enter the concept 426373005

(“Relapsing remitting multiple sclerosis (disorder),” n.d.)(Relapsing remitting multiple sclerosis (disorder)).

Although the UKMSR’s data dictionaries resolve to their own coding format, are easily accessible (“UK MSR Data Dictionaries,” n.d.) and use well published data items such as NHS Ethnicity codes as stated above, we have been able to recode our data to satisfy these other coding nomenclatures. In the case of data sharing for one project we made use of the Maelstrom guidelines to harmonise on educational attainment for example. (Salter et al., 2020) illustrating that utility in maintaining the capture the way that we do. However, for the future we are investigating standardising our data dictionaries and capture in SNOMED to ensure that collaboration can be further optimised and that the data becomes more Findable, Accessible, Interoperable and Reusable (FAIR) (Wilkinson et al., 2016).

The importance in classifying the data captured via the UKMSR does not matter to the person entering the data pwMS/clinician or carer but does make a difference to the research utility of the data across a number of domains.

Firstly, matching to incoming NHS data would be a smoother process – if an NHS site already maintained a database of patients where data were stored in one of these formats, then prescription of the data dictionaries was easier to communicate and work with. Secondly, there was the matter of linking the captured data to routine repository data such as the SAIL databank. These repositories almost exclusively make use of ICD/SNOMED or READ (UK general practice data) nomenclatures for the descriptions of their data. Having the ability to easily match captured data to these standards increases the ease of matching and having readily workable datasets. Thirdly, when working with international collaborators, having a well-defined dataset that they are familiar with makes it more understandable to the researchers carrying out the analysis, which in turn also makes working with that data more accurate. G35 in a Swedish dataset means the same thing in a UK one - making for more translatable and accurate results.

This ambition to make these types of data more FAIR as they are intended for re-use as part of scientific discovery is a laudable one. It was not a specified design standard in the initial phase of the UKMSR but the principles of it are largely embedded. Data dictionaries, even those produced in early stages, achieve many of the principles that FAIR aspires to; they are produced in a consistent way, they are clear and identify the data that they describe, and they are accessible on demand to researchers (including in different formats if required). As described above, they are interoperable as much as is feasible based on standardised coding and validation systems but there is work to be done on applying more of the FAIR principles. While these data dictionaries have grown over time, earlier versions are always available and have formed part of the data management protocols for the study. The ‘re-use’ of data is a fundamental part of the MS Register platform's design in the development of governance and the MS Register Secure e-Research Platform. I have also remained cognisant of the development of more standardised approaches to the structure and analysis of health-related datasets – effectively the specification of a common data model for research and collaboration. One of the best examples of this is The Observational Medical Outcomes Partnership (OMOP). This is an international collaboration that has been evolving alongside the UKMSR and remains a point of intense interest in better specifying the data

model that the Register uses. OMOP is one aspect of Observational Health Data Sciences and Informatics (OHDSI) and an increasing number of health informatics projects are moving towards this model.

Patient portal

A basic technology stack was architected utilising Microsoft SQL Server as a backend database, with the frontend 'website' created using a mixture of JQuery and C# code in Visual Studio 2010. These technologies were familiar to the developers creating the Register portal and allowed a level of customisation and interactivity for end users so that the website would be both clear and achieve usability levels for screen readers, or other assistive computer devices allowing end users to interact with the Register given a variety of potential disabilities. Crucially the design was made to be 'reactive' (Geiger et al., 2010) so that the site was usable on both smartphones, tablets, and desktop computers.

Patient Reported Outcomes

Assessing the impact of multiple sclerosis on a patient and their activities of daily living would be a fundamental question for the UK MS Register. Outcomes in MS had traditionally been clinically assessed, primarily through the clinician assessed Expanded Disability Status Scale (EDSS) which has been the main ‘standard’ for describing MS disability since its publication by Kurtze in 1983 (Kurtzke, 1983). This ordinal scale that requires a suitably trained clinician to carry out the assessment rates a patient from 0 (no disability) to 10 (death due to MS). It is scored by functional system (cerebellar, pyramidal etc.) and the sub scores within each system count towards an overall score. This became the default scoring system to describe change in disease in both clinical practice and in reporting on trials. Continual research and advancements in MRI technology has also brought new outcome measures as there are also now a large number of potential MRI based outcomes (Filippi and Agosta, 2010) such as T2 Lesion Load (TLL) (Daumer et al., 2009) or Brain Volume Loss (BVL) which while useful as supplemental outcomes to EDSS correlate very strongly with it.

As with all measures there are limitations to both EDSS and the radiological outcomes. By its nature a formal EDSS score in clinic is time consuming (up to 45 minutes) and requires an experienced examiner. The psychometric properties of the scale were not assessed by Kurtze but have subsequently been shown to have variable inter-rater reliability but excellent intra-rater (Sharrack et al., 1999). The issues around EDSS are well know, it typically follows a bimodal distribution (Brownlee et al., 2023) is not very sensitive to clinical change (Sharrack et al., 1999) and suffers from floor and ceiling effects (Hobart et al., 2000). Furthermore it does not assess all the domains that a comprehensive disease register should collect such as overall quality of life, health economic values or fatigue.

As for the radiological outcomes, they remain useful, but supplemental to EDSS in many clinical trials. Fine grained analysis of outcomes such as BVL requires that patients are placed in the same MRI scanner running the same software for the duration of the trial. TTL is complementary to EDSS (Filippi et al., 2012). Though the field continues to develop and more trials are making use of MRI based outcomes their limitations can be problematic.

Clinically the UKMSR would have to seek EDSS scores from patients as an outcome. For

the patient reported side we went through a process of assessing which outcome measures were in use at the time (Noble et al., 2012) and from these in consultation with academics, clinicians and pwMS we arrived at a short list of outcome measures that could be regularly asked without becoming burdensome. Unlike EDSS within every domain there are a large number of PROs that could potentially be asked in each domain - some are generic and can be applied to any disease and some are MS specific. An illustration of this would be the Multiple Sclerosis Impact Scale 29 (MSIS29) (Hobart, 2001) or the Multiple Sclerosis-Quality Of Life 54 (MS-QOL-54) (Vickrey et al., 1995) where they both have basis in other scores (MSIS is based on EDSS) MS-QOL contains elements of the SF-36 (Short Form 36 item questionnaire) but are specifically validated measures in MS. For the UKMSR the MSIS-29 was selected for MS, the EuroQOL 5-Dimension level 3 score (EQ5D-3L) (Brooks, 1996) for general quality of life, health economics and comparison with other disease cohorts. Lastly the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was chosen for assessment of overall mood and mental health.

Later in the development of the UKMSR we added an instrument for fatigue - The Fatigue Severity Scale (FSS) (Krupp, 1989) and a web based variant of the EDSS score the webEDSS (Leddy et al., 2013). Adding all of these instruments and asking them consistently would allow the Register to holistically assess the participants of the UKMSR - beyond the largely disability only assessment of the clinical EDSS score.

NHS data collection

The NHS data collection was architecturally more simplistic: SQL Server would also be employed as a backend, but the existing Secure Anonymised Information Linkage (SAIL) (Ford et al., 2009) switching service could require authenticated users, restricted by Internet Protocol address, to upload comma separated value (CSV) files, or Excel spreadsheets (XLS) from any bespoke system that a Trust had. It is worth stating that the earliest iterations of the Register were anticipating authenticated data transfers from inpatient hospital systems utilising HI7 or other well-specified technology stacks. However, the wide array of technology available across the NHS made this challenging, with data ultimately being transferred via Secure File Transfer Protocols and other slightly more user-intensive technologies. These were the methods most acceptable and widely understood by NHS trust ICT staff, following the attainment of relevant governance approvals for the transmission of consented identifiable patient data.

SeRPs governance and third-party researchers

A goal that was never explicitly outlined in the tender from the MS Society was the further use of data captured by the UKMSR. It seemed obvious to me that if a register were to be created into which diverse longitudinal datasets were being added, and that this data would be useful to researchers at Swansea University, then it would also have value to other researchers in multiple sclerosis too. More than that, making it available to others would prevent people with MS and NHS sites from having to submit the same responses to similar questionnaires time and again, or send data to similar studies in MS. I made a decision that the Register could serve as more than just a destination for data, but that those datasets to be captured could be specified by third-party researchers and then pseudonymised data

would be made available to them. This required a number of items in place to make it a reality.

1. The ethics of the UKMSR should be flexible enough that in the correct circumstances we could federate ethics from other studies as part of our work. Allowing for the recruitment of participants to sub-studies or for particular questionnaires without having to revisit the national ethics research service every time.
2. Applications to make use of Register data or distribute questionnaires should be reviewed by a panel of experts, on which the MS Register researchers did not get a vote - merely the capacity to indicate whether a study was feasible or not.
3. Data made available to third-party researchers should be pseudonymised and exist in a repository where line-level data cannot be removed and can only be utilised by appropriately qualified researchers. These data to be archived and accessible beyond the duration of their projects for the purpose of replicability.

Following the initial pilot period of the UKMSR I established, with collaboration from the MS Society, a Scientific Strategy Committee that would be responsible for vetting research requests and approving or denying them as was appropriate. This group consists of people with MS, academic neurologists from other institutions or international registers, and a representative from the MS Society as the primary funder. These members meet quarterly to assess the quality of new applications and vote on approval of this research.

Once approved, researchers had to complete a course on the General Data Protection Regulation (GDPR) and safe researcher training, their requested datasets were loaded in the MS Register Trusted Research Environment (TRE), known as a SeRP (Secure e-Research Platform) (Jones et al., 2016) a secure remote desktop environment in which all the tools required to carry out research were present such as MATLAB, SPSS, SAS, R and Python and analysis could be performed. The advantages of such an environment are clear – the data resides in one place and where new data is made available for those researchers, it can be rapidly provisioned and linked within the environment. Crucially, it is given a new version number so that any data that has been analysed is distinct. This ensures that there are no ‘old copies’ of data extant in the world. There is a central location for it. Desktops are archived should researchers need access to their analyses at a later date. Aggregate data can be removed as part of ongoing research but data with counts of less than five cannot. Most of the papers in Appendix 1 have been produced by external researchers making use of UKMSR data in this way.

My input

As the System Architect of the UK MS Register, it was my role to design, develop and implement a platform that at the bare minimum could capture the requirements as stated by the funders, but ideally should comprise an awful lot more as evidenced in the text above. In the papers below I outline my role in the design and construction of the UK MS Register, through the narrative of papers in peer-reviewed journals. In parallel to this, I felt it was essential to author and enable the production of a number of papers that would illustrate how the UK MS Register was conceived, its datasets produced, its methods for recruitment, how data were captured, how the participants were validated and how it could deal with novel datasets and research concepts.

Bringing together this need to capture Register data, electronically, to specified dataset standards, to extensively incorporate patient ‘voice’ as a primary input and to make this captured data easily accessible to other MS Researchers to truly create MS Register platform for all stakeholders in MS was my ambition.

Chapter 2: Desirability and expectations of the UK MS Register: views of people with MS

Background

This chapter starts with the earliest days of development of the MS Register. The paper below was published in the International Journal of Healthcare Information Systems and Informatics, and outlines what the participant population might expect from a putative MS Register, before a line of code had been written for its development. It was important even from the genesis of the Register that it would not be an entirely clinical or researcher-only dataset, but that it would be relevant to, and purposeful for, the people that would be asked to regularly complete questionnaires.

As System Architect, I had outlined the notional MS Register with a design centring around collecting data from people with MS via the internet, directly from NHS hospitals via clinical systems, and then linking this data richly with other sources of 'routine data' such as the SAIL databank. The specifics of what should be collected, however, were still very much to be decided. Although, as stated in the introduction, there were some 'obvious' data items that should be collected, many details, and even the methodology of using the internet to capture data from PwMS, had to be established through research. We therefore designed a study that would make use of concept analysis to understand the requirements of potential participants.

My input

As second author this was my first exposure to qualitative analysis. I was extensively involved in the question-setting, literature review and editing of the manuscript. As the architect of the MS Register, the results of this research were crucial to it being established in a way that was compelling to people with MS and which answered some of the desires that they raised as part of this process.

Aim

To establish what people with MS expected and required from a putative MS Register.

Method

The study was designed to be carried out by telephone, to prevent participants having to travel and to ensure they were in familiar surroundings. There were three key questions and seven related ones. Additionally, we collected demographics from the participants to ensure that they were representative of people with MS in the UK.

Participants were not offered incentives to take part in the study and were recruited from local MS groups, adverts on MS Society forums and via word of mouth. The survey design was qualitative and would primarily focus on a telephone interview, so as to not bias against those with no access to, or familiarity with, the internet. Participants were recorded and all

interactions were carried out by the same researcher. There were three key questions to participants around:

1) The desirability of the Register;
2) What the participants envisaged the Register actually being used for;
3) What they hoped the Register would be used for;

and seven more questions designed to elicit further detail. We carried out concept analysis on all responses, codifying them into positive and negative (concerns) categories for questions two and three, and a conditional 'could be' category for question one.

Results

There were 312 responses from 23 people with MS (16 female, 7 male), mean age 51.7 (SD ±7.7; range 37-64) years, with both progressive and relapsing types of MS. Participants with a range of disabilities were invited to take part in a telephone study in order to establish their views on an internet-based register for MS.

We could not accommodate everything that people wanted in the first iteration of the MS Register. For example, serving as a resource for carers to exchange pointers or tips was outside of the scope of the data to be collected. All of these desires had to be balanced with the overall aims of the Register – that is, to capture high-quality data suitable for research, and ultimately contribute to clinical decision making. This work also set in motion the involvement of people with MS in all aspects of ongoing design of the MS Register. At this point in time, for most research projects, participant/patient involvement (PPI) was seen as largely peripheral to the overall goals of the project. In many aspects of the Register we have moved towards co-creation with people with MS, not just 'involvement'.

https://doi.org/10.1016/j.ijmedinf.2013.07.005

Conclusions

Although the output of this work was based on a relatively small sample of pwMS, the results illustrated the key points of what they may want from a register, and what they thought that they may actually get. Fundamentally, pwMS were broadly positive about the concept of a register – subject to valid concerns around security, privacy and how specific the information may be to the individual in such a broad data collection initiative. The primary point that came across was a strong desire that a register should have utility for *research* and that concept was applied across a range of areas, such as patterns, causation, and comparison between types of MS. There was also a strong theme that information captured should be useful for service planning within the NHS, and for campaign planning for the charities involved. A smaller theme emerged around the potential use of a register for social networking. Respondents believed a register would be useful for research and for recruitment to research.

Hearing that the MS Register was not only acceptable, but desirable, to people with MS, was extremely encouraging. This platform had to serve a number of disparate functions, while still having demonstrable utility to pwMS. The 'problematic' concerns raised by some interviewees – primarily that it may not be useful, or serve as a resource for those that had no (or limited) internet – were acknowledged as potential issues. Given the growth of internet use across all age groups (since 2011, internet usage in the over 65 group has seen the fastest growth of all internet users (Cecil Prescott, 2016)), this limitation, even in 2011, was only expected to affect a very small proportion of the population. Ultimately, having clear goals from pwMS around their expectations for elements such as improved data around counts of people in the UK by MS type or surfacing information for better MS service planning in the NHS made the mission of creating an MS Register that had a broad approach to its collection of information more powerful.

This paper directly influenced methods used in the creation of the first version of the MS Register. For example, while security and privacy were always going to be treated to high-level standards, the results of the interviews helped us better understand the importance of being explicit about these standards when communicating with participants. It also helped crystallise the idea of putting the PRO data at the centre of the MS Register and the novel utility that linkage to that data could bring, beyond simple statistics and improved information about prevalence of certain types of the disease. Though these were features of the initial ‘pitch’ of the Register to the funder, the expanded aspiration for more data linkage and enhanced functionality were of keen interest. Participants had highlighted that a register should be useful to them, it made sense that it would have utility to all the other stakeholders too. The need to capture data that would be relevant to participants and not just researchers and clinicians would be a significant feature of the production Register.

This initial paper established a way of working with people with MS from the outset – we would embed pwMS in almost every aspect of the UKMSR and their crucial input to the development of the working Register is revisited in Chapter 7.

Chapter 3: The feasibility of collecting information from people with multiple sclerosis for the UK MS Register via a web portal: characterising a cohort of people with MS

Background

Having been informed by my first paper on what pwMS desired and expected from an MS Register, I set about its actual construction. There were numerous issues, both technical and procedural, that had to be solved to get to the point of data collection. These included vital elements such as finalising and submitting the protocol and the initial dataset for ethical consideration to the South West Central Bristol research Ethics Service. Alongside this was the need to architect database backends in SQL server, and decide the 'front end' programming language that the portal would run via Internet Information System and Active Server Pages. All of this achieved, the Register ‘portal’ formally launched in 2011 and data collection began. At the time of writing the paper only one round of data collection had been carried out (cross-sectional) though the intention was always for the Register to be longitudinal.

My input

Although listed as the third author on this paper, it clearly illustrates the concepts that were required to be brought together to build a functioning Register, and that even in this pilot stage, the Register could perform as specified. My work for this paper comprises the architecture of the data collection system, data collection itself, analysis and interpretation of baseline demographic data, and editing iterative drafts of the manuscript.

Methods

The choice of instruments had been decided through academic research by my team (Noble et al., 2012) and in co-creation with pwMS, academics, representatives from the MS Society, and clinicians. We needed to ensure that those outcome measurements selected could be collected at scale using the architected system.

Data capture via the portal fell into two broad areas: straightforward demographic and epidemiological instruments, and PROs. The mission of these questionnaires varied slightly, with the PROs designed to be captured repeatedly in a three-month rolling 'window'. As soon as an instrument was completed by a participant, a countdown timer would start on a database. Once this three-month period elapsed, an email would be sent to that participant reminding them to come back and complete that PRO again. The demographics and epidemiological questions (as infrequently changing information) were designed to be used intermittently.

The UKMSR launched with a number of 'core' PROs; the Multiple Sclerosis Impact Scale 29 (MSIS-19), the Hospital Anxiety and Depression Scale (HADS) and the EuroQol-5D-3L (EQ5D). The selection of these instruments was to allow for disease-specific data (MSIS), a

general quality-of-life instrument that was well known for its utility in calculating health economic impacts (EQ5D), and an instrument to assess anxiety and depression (HADS). These, combined with the demographic, diagnosis, and disease course data from the UKMSR questionnaires, would form a baseline study and would give a useful insight into living with MS in the UK that had not been seen before.

Relatively high counts of missing data (including more than 4000 participants without location data) would be addressed in later versions of the Register by increasing the number of mandatory fields; delaying this until after the first round of data collection allowed us to assess response levels and participant burden. In later communications with participants and in wording on the website we also stressed that this was an ongoing study – not just a snapshot in time. We also recognised that the cohort would have to be validated as actually having multiple sclerosis. This validation process, carried out through data linkage, is described in detail in chapter five.

Results

The UKMSR web portal launched to the public in May 2011 following a media campaign from the MS Society that included TV and radio segments on local and national news stations. Within three months 7,279 participants had enrolled on the portal, though not all of these had completed sufficient data to form part of an analysis. Mean age at registration was 50.8 (SD±11.4), with a gender ratio of 1:2.4 (male:female). 63% of participants indicated that they had RRMS, 15% PPMS, 8% SPMS and 14% were unsure of their MS type. Mean age at onset was 34.0(SD±10.5) and mean age at diagnosis was 39.4(SD±10.1) years.

A factor that altered the Register very directly was the response via alternative login methods. In 2011 I had thought a critical way to get engagement with participants was to offer them alternative logins via the MS Society's forums (if they had a pre-existing account) or from Facebook. Even at this early stage it was apparent that participants did not want to make use of a social media account when logging into the Register, with only 1% of respondents electing to use this method.

Another, perhaps more pressing, matter that I went on to try and address in the next iteration of the Register was the comparatively large amount of seemingly 'missing' data. The number of people that elected to not give a location (n=4,428), for example, could be traced to a decision to not make many of the fields for collection mandatory. It was felt that it may put people off, increase cognitive load, or cause increased frustration. Though a well-meaning decision, this did lead to some initial scepticism about how robust the data collection actually was – although later work would prove this not to be the case. Through learning with the community about what would be acceptable, location and other similar fields were changed to be mandatory.

This study represented a much larger population than those surveyed in Paper 1, and the sheer numbers of people willing to take part in such a new platform emphasised the desire in the community to contribute in a very personal way to research.

Paper 2: The feasibility of collecting information from people with multiple sclerosis for the UK MS Register via a web portal: characterising a cohort of people with MS

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The feasibility of collecting information from people with Multiple Sclerosis for the UK MS Register via a web portal: characterising a cohort of people with MS

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Abstract

Background: A UK Register of people with Multiple Sclerosis has been developed to address the need for an increased knowledge-base about MS. The Register is being populated via: a web-based portal; NHS neurology clinical systems; and administrative data sources. The data are de-identified and linked at the individual level. At the outset, it was not known whether people with MS would wish to participate in the UK MS Register by personally contributing their data to the Register via a web-based system. Therefore, the research aim of this work was to build an internet-mounted recruitment and consenting technology for people with Multiple Sclerosis, and to assess its feasibility as a questionnaire delivery platform to contribute data to the UK MS Register, by determining whether the information provided could be used to describe a cohort of people with MS.

Methods: The web portal was developed using VB.net and JQuery with a Microsoft SQL 2008 database. UK adults with MS can self-register and enter data about themselves by completing validated questionnaires. Descriptive statistics were used to characterise the respondents.

Results: The web portal was launched in May 2011, and in first three months 7,279 individuals registered on the portal. The ratio of men to women was 1:2.4 (n = 5,899), the mean self-reported age at first symptoms was 33.8 (SD 10.5) years, and at diagnosis 39.6 (SD 10.3) years (n = 4,401). The reported types of MS were: 15% primary progressive, 63% relapsing-remitting, 8% secondary progressive, and 14% unknown (n = 5,400). These characteristics are similar to those of the prevalent MS population. Employment rates, sickness/disability rates, ethnicity and educational qualifications were compared with the general UK population. Information about the respondents' experience of early symptoms and the process of diagnosis, plus living arrangements are also reported.

Conclusions: These initial findings from the MS Register portal demonstrate the feasibility of collecting data about people with MS via a web platform, and show that sufficient information can be gathered to characterise a cohort of people with MS. The innovative design of the UK MS register, bringing together three disparate sources of data, is creating a rich resource for research into this condition.

Keywords: Multiple Sclerosis, Disease register, Data linkage

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Background

Multiple Sclerosis (MS) is a degenerative neurological disorder that is estimated to affect around 85,000 to 100,000 people in the UK [1,2]. Programmes for treating and managing MS should be underpinned by robust data, but it has been recognised that there is a significant lack of reliable, evidence-based information to inform service delivery and to generate important health service research on MS in the UK [3]. This may be due to a number of factors such as the prolonged disease course, evolving over several decades [4], and difficulties or delays in diagnosis, as people may present with a wide variety of symptoms [5]. To date, there is no central repository for MS data in the UK. There are a number of different database systems in MS treatment centres, but no agreed data model and no network and policy infrastructure for sharing data between NHS settings [3,6]. In response to this, the MS Society of Great Britain and Northern Ireland [2] commissioned the development of the UK MS Register.

The aim of the work was to build a working prototype MS Register, for use in 5 centres across the UK, capable of being scaled to a national deployment. There are two clinical sites in England, one in Wales, one in Scotland and one in Northern Ireland. The Register has been designed to capture three main categories of data and to be able to anonymously link these data at the individual level whilst retaining privacy. Data are collected directly from people with MS via a purpose-built web portal, from patient-management systems operating in NHS neurology clinics, and from sources of routine administrative data (such as primary care and hospital data). Numerous datasets may be included in each of the three categories. There are other national registers for people with MS such as in Denmark, Norway, Sweden, Italy, Germany and North America [7]. However, these collect data from only one or two of these categories, though this may include multiple datasets. By uniting datasets from three disparate categories the UK MS Register model is innovative in its design and provides new opportunities for studying MS via linked data. The Register is operating initially a prevalence-based register, but as we continue to collect data, with regular updates from the different sources, we will be able to estimate incidence. Our aim is to create a UK population Register of people with MS, with as complete coverage as can be obtained whilst acknowledging that participation is voluntary. This register model could also be applied in other disease conditions.

Research aim

At the outset of this work it was not known whether people with MS would wish to participate in the UK MS Register by personally contributing their data to the Register via a web-based system. Therefore, the objective of the work described here was to build an internet-mounted recruitment and consenting technology for people with MS, and to assess its feasibility as a questionnaire delivery platform by determining whether the information provided could be used to describe a cohort of people with MS. In order to do this, we provide a description of the development of the portal and the self-reported characteristics of its first cohort of people with MS.

Methods

Research ethics and governance

The UK MS Register study was granted ethical approval by the South West – Central Bristol Research Ethics Committee (11/SW/0160) under the category of a research database [8]. The Register has been based on the proven technologies and robust Information Governance arrangements in place in the Secure Anonymised Information Linkage (SAIL) system developed by the Health Information Research Unit (HIRU) [9,10]. HIRU aims to realise the potential of electronically held, person based, routinely collected information and to bring together expertise in health informatics to support and conduct research. The SAIL databank holds multiple, disparate person-level datasets drawn from operational and national systems, and over 2 billion anonymous records have been loaded to date. Novel anonymisation, encryption and linkage processes have been developed to manage and link datasets securely, so that the SAIL databank is an extremely successful method of accessing linked data from individuals while preserving their anonymity. Under the ethical approval that has been obtained, data collected via the portal, the neurology clinics and routine administrative sources can be anonymously linked using the SAIL methodologies provided that agreement to the portal terms of service (via the portal) and written informed participant consent (at the clinics) have been obtained. The consent process at the neurology clinics is for the provision of identifiable data to the Register, so that the identifiable details can used to enable record linkage. Datasets are linked at the individual level using first name, surname, date of birth, gender and postcode as the matching variables, and then a unique anonymous identifier is assigned to each individual in the dataset to act as a linking field across datasets. This, together with a de-duplication process, ensures that each person is included on the Register only once. The working UK MS Register contains only anonymous data but facilities are in place to re-contact participants to take part in further research.

Development and implementation of the web portal

Although the development of the portal is embedded in the SAIL system, it is not specific to SAIL. It uses commonly used toolsets and other systems could equally form the basis of such a portal, either as part of a register or standalone. The portal was developed in Visual Studio 2010, deployed on Microsoft IIS (Internet Information Services) and the data are stored securely in

Microsoft SQL Server 2008. The interface elements of the portal are a mixture of HTML and JQuery which is a Javascript library. This mix of technology was used to allow a deeper level of interaction and feedback to the portal users. There are three routes by which people with MS can access this questionnaire-delivery platform: via the standalone register web portal [11], through the MS Society website (available to members of the Society [2], or via a purpose-built web application on Facebook [12]. These entry options are designed to boost recruitment and are ultimately all routed to the questionnaire-delivery platform. People who use the main Register web portal are directly authenticated via the portal. Users select their own usernames, which must be unique, and passwords are stored as salted hash elements within the database, providing a high level of security. The second method makes use of an authentication token from the UK MS Society website. In this case, no identifiable details are transferred between the MS Society and the Register portal, just the token. This allows members of the Society to join the Register without having to remember an additional user name and password. Once logged in and registered, an XML message is returned to the MS Society member. This is displayed to them as an interactive element that allows them to return to the Register at will whilst logged in to the MS Society site. The final method of authentication is via the Facebook social networking site. Web developers within Swansea University created a Facebook application via the published guidelines [13]. Again, only authentication information is provided and no personal or clinical information is shared with Facebook. Users must be logged into Facebook and agree to install the Register application. They then access the Register from the link that the application installs in their Facebook profile.

Following the development process a demonstration portal was implemented for usability testing and improvement. Feedback on its utility was obtained from people with MS and key stakeholders, including clinicians and representatives of the MS Society before the portal was formally launched to the public. The work on usability testing is the subject of another article which is in preparation. The launch of the portal was marked by a nationwide advertising campaign by the MS Society and mailings to MS Society members, radio and TV broadcasts and national newspaper articles [14,15]. People (over 18 yrs) with a diagnosis of MS and living anywhere in the UK are eligible to register on the web portal. Participants must have a functional email address and to be able to agree to the terms of service.

Data collection and analysis

The web portal collects demographic data from people with MS and hosts a number of validated questionnaires. These instruments were chosen following a literature review and discussions with key stakeholders, including neurology clinicians, people with MS, researchers and the MS Society. They include the Hospital Anxiety and Depression scale [16], the MS Disease Impact Scale-29 [17], and the EQ-5D [18], covering a range of topics such as: MS and mental well-being; MS and quality of life; MS and lifestyle; and medication records. The questionnaire entitled 'You, your MS and lifestyle' collects baseline information about MS including: date of diagnosis of MS, type of MS and age at onset, plus information on education, employment and living arrangements for people with MS. Recruitment to the web portal is on-going, and people who register are sent an email every 3 months inviting them to return to the portal and update their questionnaires to build up a longitudinal data source.

The responses to 'You, your MS and lifestyle' (obtained between May and July 2011) were used as the sample for data analysis in this work. They were collated with the basic demographic characteristics (such as age and gender) required to register on the portal in order to be able to explore various factors about living with MS. Following quality assurance, the resulting anonymised dataset was analysed (in SPSS v.16) using descriptive statistics to show the sort of information that can be collected and to provide a general profile of the first cohort in the UK MS Register. The characteristics of the respondents were compared with published reports on the prevalent MS population, and employment profiles, ethnic composition, and highest educational attainments of people with MS were compared with the general UK population [19-21].

Results

The web portal was successfully launched in May 2011 and within three months 7,279 individuals had enrolled on the MS Register via the web portal. Taking into account that there are estimated to be between 85,000 and 100,000 people with MS in the UK [1,2], this represents an approximately 8% sample of the prevalent MS population. Of these respondents, 97% entered directly via the stand-alone website, 2% registered by way of the UK MS Society website, and 1% registered through the use of the Facebook application. Once registered, people can choose whether to provide additional information via completion of the questionnaires. This work relates to 'You, your MS and lifestyle' and majority went on to complete this questionnaire. As this questionnaire contains disparate questions, and is not an assessment tool that produces an overall score, it is not necessary for it to be completed it in its entirety in order to be able to use the data. The rate of responses ranged from 61% (UK country of origin) to 82% (types of first symptoms) and numbers of responses are shown in the text with the relevant results.

Demographics

There were 3,290 respondents who stated they lived in England, 619 in Scotland, 342 in Wales and 177 were of

unknown location (n = 4,428). The ratio of male to female respondents was 1: 2.4 (n = 5,899) and there was a broad age range among the respondents at time of enrolment: 18 to 95 years, with a mean age of 50.8 (SD 11.4) years and a median of 50.0 years. The ethnic composition of the group (n = 5,780) was largely White British (93.8%) with a variety of other ethnicities making up the remainder.

MS and diagnosis

MS is classified into different types depending on the characteristics of the disease course. The majority of patients are initially diagnosed with relapsing-remitting MS (RRMS), but this may change over time [2]. Of the respondents that provided their information on this (n = 5,400), 15% reported having primary progressive MS (PPMS), 63% stated that they had RRMS, and 8% had secondary progressive MS (SPMS). The remaining 14% did not know which type of MS they had. The distribution of reported type of MS by gender is shown in Figure 1. It can be seen that relatively greater proportions of men report that they have a progressive type and relatively greater proportions of women report having RRMS. A first-degree family member (parent, sibling or child) with MS was reported by 8.5% of the respondents. Of these 4% had a parent who had MS, 4% had a sibling with MS, and 0.5% stated that they had a child who developed MS.

The mean age at which the respondents recalled first experiencing symptoms of MS was 34.0 (SD 10.5) years (n = 4,918), and the mean age at which their diagnosis was confirmed was 39.4 (SD 10.1) (n = 4,883). The mean time since their diagnosis was confirmed was 11.4 (SD 8.9) years with a range of 0 to 63 years. This indicates that our sample contains a breadth of respondents spanning recently-diagnosed and long-term. Although there is no definitive list of early MS symptoms, the ones experienced by the respondents (n = 5,969) were among the most common: [2]

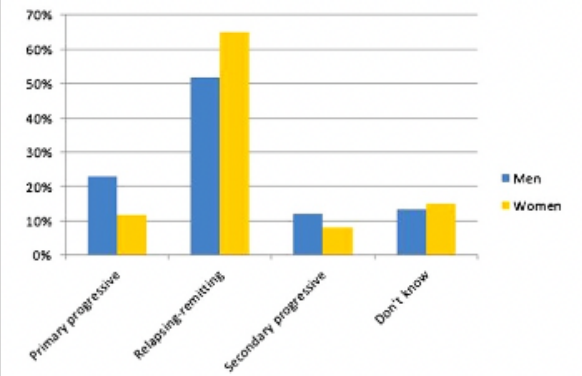

Figure 1 The distribution of types of MS by gender. People with MS provided information on the type of MS they have been diagnosed with. The proportions are indicated here, grouped by gender.

67% had difficulty walking, 65% experienced numbness, and 59% had vision problems. These symptoms were sometimes present in combinations: for example, 25% of respondents reported experiencing all three effects and only 2% reported that they did not experience any of these symptoms. A Venn diagram showing the proportions of people with MS experiencing the various combinations of these symptoms is shown in Figure 2.

People with MS reported different experiences in the process of their diagnosis. However, in accordance with the McDonald criteria [22,23], the majority received an MRI scan (79%) and in 29% of cases this was used in conjunction with CSF (lumbar puncture) and clinical findings. Less than 4% (3.7%) did not recall receiving either of these and stated that they were diagnosed from clinical findings alone. Most people (79%) were given the diagnosis of MS by a consultant neurologist, 19% by a consultant physician and less than 2% by a general practitioner (n = 5,736).

Education and employment

The respondents were asked about their highest educational achievements. Among the 5,819 respondents, the largest single qualification was an occupational certificate or diploma (34%), a third (33%) attained a university bachelor or postgraduate degree, just over a quarter (26%) were educated to secondary school level and only 0.2% left school after primary school. The remainder (7%) indicated that they had miscellaneous qualifications or overseas education (Figure 3).

The people with MS were asked about their usual occupation and the resulting profile (n = 5,046) was compared with the actual employment profile of the general UK population using the official labour market categories for 2010–2011 (Table 1) [19]. It can be seen that in some categories the respondents usual occupations are similar to the actual figures for the UK, and in others, they differ. It should be noted that this compares usual with actual occupations, and our sample consists of approximately 30% men and 70% women, whereas the UK workforce is approximately 54% men and 46% women [19].

The responses on actual employment status showed that 36.9% of the sample were in employment, which equates to 41.9% of the people of working age, and of these, the majority were in part-time work (88%). By comparison, 76.9% of the general UK population (aged 16 to 64 years) are economically active [19]. Almost a third of the respondents (29.8%) reported that they were sick/disabled, equating to 32.7% of working age, with the majority reporting that they are permanently (rather than temporarily) sick/disabled (91%). This is higher than the 24.5% of the working-age UK population recorded as being sick/disabled [19]. The differences in the employment and sick/disabled rates between people with MS and the general UK population show the impact of MS on the UK workforce.

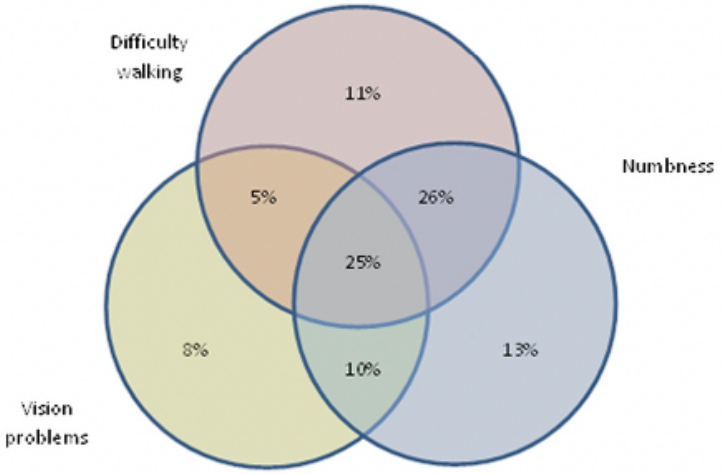

Figure 2 Initial symptoms experienced by people with MS. People with MS were asked to indicate whether they experienced numbness, difficulty walking or problems with their vision, or combinations of these symptoms, among their initial symptoms of MS.

Over a fifth of the respondents (22.4%) reported that they had retired, and this equates to 86% of the over 65 s age group. The remainder of the respondents were engaged in activities such as education, home-making or voluntary work, or they gave their status as unemployed.

The distributions of the types of MS among the people who were employed were compared to those of people who were sick/disabled. Among the employed respondents 20.3% reported having PPMS, 40.4% RRMS, 10.0% SPMS and 29.3% did not know which type of MS they had. This indicates that, as might be expected, higher proportions of people with RRMS are in work compared to the progressive types of MS. Among the sick/disabled respondents there were 27.6% with PPMS, 20.9% with RRMS, 31.9% with SPMS and 19.6% did not know their type of MS. This is the converse, as it shows that greater proportions of people with a progressive type of MS are sick/disabled compared to people with RRMS.

The employment rate among the respondents who reported that they were working (<=64 for men and < =59 for women) was assessed against the length of time since their MS was diagnosed (in 5 year bands). As would be expected, this showed that the proportions of people in employment declines with increasing time since diagnosis (Figure 4). For example, over 40% of the people who are working have a recent diagnosis (0 to 4 years), and only approximately 2% of the people who are working have been diagnosed for 25 years or more. A similar analysis was conducted to assess the rate of sick/disabled respondents of working age and, as would be expected, this showed a steady increase in cumulative proportions by time since diagnosis (Figure 5).

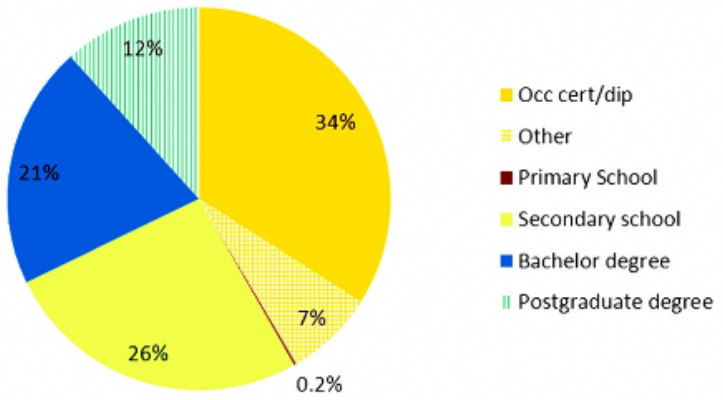

Figure 3 Highest educational attainment reported by people with MS. People with MS provided information about their highest educational attainments.

Table 1 Usual employment types among people with MS

Employment type	Respondents %	UK %
Administrative & secretarial	22.8	10.7
Associate professional & technical	10.4	14.7
Caring, leisure & other personal service	3.9	8.8
Elementary occupations	1.9	11.3
Managerial, director or senior official	15.6	15.6
Process plant/machine operatives	1.2	6.6
Professional	30.5	14.1
Sales & customer service	7.2	7.4
Skilled/trade	6.4	10.3

People with MS provided information on their usual type of occupation. This is compared with the actual employment profile for the UK population (2010–2011). These profiles are discussed in the text.

Household arrangements

There were a wide range of living arrangements among the respondents (n = 5,604). The most frequently reported household settings for the people with MS were as: an adult couple not on a pension and with (non-dependent and/or dependent) children (25%); an adult couple on a pension with no dependent children (23%); an adult couple not on a pension and with no children (16%); and a single pensioner (15%). Some respondents in adult couples reported that they live in households with other relatives or unrelated adults (8%). Altogether there were 31% with dependent children and 3.3% were single parents with dependent children.

Discussion

Main findings of this study

The main findings of this study are two-fold. Firstly, we have shown that it is possible to collect information from thousands of people with MS via a web-based questionnaire delivery platform. Secondly, sufficient information can be gathered to characterise a cohort of people with MS to feed into the Register. This provides new information about the lives of people with MS in the UK from their own perspective. This is encouraging as it supports the continuance of collecting information for the UK MS Register via this route, and this design could be used to set up a similar portal to collect data from people with other conditions.

What is already known on this topic

There are numerous research programmes seeking to understand the possible causes of MS and to develop drug therapies to manage the condition. However, it is acknowledged that there is a great shortage of information to guide service delivery and research about MS [3], and this led the MS Society to commission a UK MS Register. It is estimated that (in 2008) there were approximately 85,000 people with MS in the UK, with a mean age of onset of 32.5 years, and gender proportions of 1:2 to 1:3 male to female [1,2].

Data validity

Through the analyses we have conducted we have shown that we have a broad sample of ages and MS durations and that our respondents are reasonably representative of the prevalent MS population. The gender proportions, mean age at onset, proportions of MS types, and the distribution of types of MS by gender in our findings are similar to other reports [1,2,24]. We cannot yet estimate prevalence from this initial, unlinked dataset, but we will be able to do this in the near future when we are able to link portal responses with other sources of data.

We compared various features of the sample with the general UK population. In the 2001 census, approximately 85.7% of the UK population reported that they were White British, and 91.4% White British/Irish/Other, with the remainder being made up of various ethnic groups [20]. There may be minor changes in the UK population over time since the census was taken but the higher proportion observed in our sample (93.8%) is not

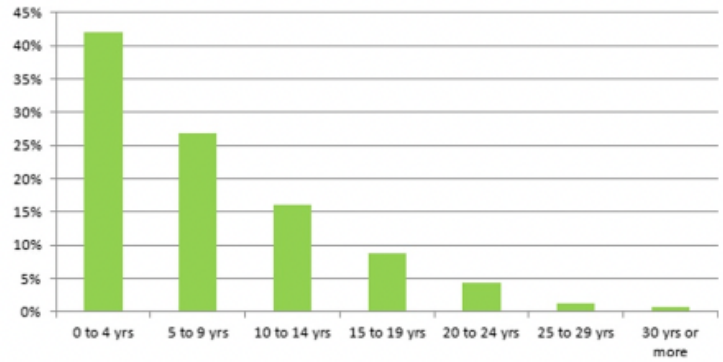

Figure 4 Employment rates by time since diagnosis. Proportional rates of employment for people with MS of working age were assessed against the duration of the MS diagnosis in 5 year bands.

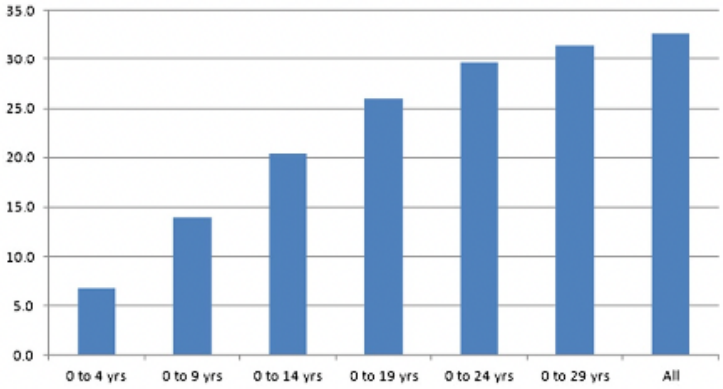

Figure 5 Rates of sickness/disability status by time since diagnosis. This shows the cumulative percentage of people with MS of working age reporting their status as sick/disabled by length of diagnosis (in 5 year bands).

unexpected as higher rates of MS are reported in White populations [25]. The respondents were similar to the UK population in highest educational attainment. The UK Labour Force survey for 2011 showed that 31% held a first degree or a higher degree, and 29.3% did not progress beyond secondary education [19]. In our sample 33% held a first degree or a higher degree, and 26.2% were educated to secondary level. People with MS were asked about their usual occupations and these were compared with the actual occupations of the UK workforce, and although there were some similarities, some obvious differences were seen in the occupation profiles (Table 1). The full reasons for these differences are not known at this stage. However, it is worth noting that the comparison was of usual occupations with actual occupations, and it is possible that differences would also be noted if the usual and actual occupations of the general UK population were compared, as people may work in jobs outside their usual occupation type. Only approximately 42% of our potential MS workforce were in employment and it is possible that the observed profile also reflects the types of occupation that people with MS are able to continue working in. Also, the gender proportions of our sample are different to those of the UK workforce, and this may influence the distribution of occupation types with some types of work being more common to one gender or the other. Although further work needs to be carried out to understand the occupation profiles, the analyses on employment status, namely, the distributions of types of MS among people who are working and among people who report that they are sick/disabled, and the trends in employment rates and sickness/disability rates over time are in keeping with what would be expected in a degenerative condition like MS.

What this study adds

In collecting data from clinical settings, administrative datasets and directly from people with MS, the UK MS Register has a broader data model than other national MS Registers which use only one or two categories of data [7,26]. This model could be applied to other disease Registers. The web portal provides a flexible platform for the delivery of a range of questionnaires, providing all people with MS in the UK an opportunity to contribute their data, which is of potentially great value to service planning and research. This study has provided information from people with MS on their demographics, the process of their diagnosis and the type of MS they believe they have, and on their education, employment and living arrangements.

Future work

Future work will include analysis of the responses to other questionnaires delivered via the platform, to create a fuller picture of living with MS. We will also link and compare the self-reported information with clinical and administrative data to estimate disease prevalence and to carry out further validation. Since MS can be difficult and lengthy to diagnose, we are developing a case ascertainment algorithm to use against routine data (such as primary and secondary care records). This will help us to study the anonymous routine data to profile the group of people with MS who are not on the Register and thus enable us to target further recruitment activities. We are engaging in a series of marketing activities to promote the Register and to encourage further participation, and through these methods we are seeking to ensure that the Register is inclusive and representative of the UK MS population. Furthermore, a programme of qualitative research is underway to engage with people with MS to improve our understanding of their needs in contributing to the Register. For example, we are seeking to understand their internet preferences, such as their reasons for choosing a particular portal entry route, so that we can optimise enrolment on the Register [27]. In future, the Register data will be made accessible for

analysis, subject to regulatory and governance requirements. The final operating model for these arrangements is yet to be determined.

Limitations of this study

The information used in this study was self-reported and the respondents are not necessarily a fully representative sample of people with MS in the UK. Ascertainment is commonly assumed to be skewed when using web-based methods, as the technology may pose a barrier to the elderly, disadvantaged, technically inexperienced or cognitively impaired [28,29]. Response bias in portal data will be addressable using the linkable data from clinical sites and routine sources, as the Register continues to build up an increasingly detailed picture of MS in the UK and to become a rich information resource.

Conclusions

The initial findings from the MS Register portal demonstrate the feasibility of collecting data about people with MS via a web-based questionnaire delivery platform, and show that sufficient information can be gathered to characterise a cohort of people with MS. The innovative design of the UK MS register, bringing together three disparate sources of data, is creating a rich resource for research into this condition.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the design of the project, and RMM, HL-J, KHJ and IDCM acquired, analysed and interpreted the data. KHJ drafted the manuscript and all authors revised it critically for important intellectual content, and gave their final approval of the version to be published.

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Conclusions

The system that I had architected had proven that it could collect data at scale, with more that 7,000 people creating an account and submitting responses to demographic, epidemiological, and PRO questionnaires.

This study was important to the UKMSR as it proved the theory that people with MS would participate, at scale, in a large systematic data collection exercise. More fundamentally, it demonstrated that the data collected would have utility as a snapshot (cross-sectional), even before the analysis of longitudinal data were possible. The data captured by the study were consistent with what was being observed in other disease registers around the world and in data previously collected at a smaller scale within the UK. There were of course important caveats to the participant population – the most obvious being how could I prove that a participant declaring themselves as having MS, did actually have MS? The validation step between the self-reported data, and the other data sources, was of paramount importance.

Importantly the genesis of the Register as a 'platform' was in place. We now had a trustworthy system in place, into which pwMS were happy to entrust their information – a point that had been raised in the Paper 1. Most importantly, through analysis, that data was in line with what a population of people with MS would be expected to provide to such a platform.

Chapter 4: Sunshine, sea and season of birth: MS incidence in Wales

Background

A fundamental aspect of my design of the UK MS Register was that it could make use of linked data from a variety of sources. Initially data would be linkable between the clinical and portal populations and is discussed in more detail in Chapter 5, but it would also be beneficial to link to 'routinely' collected data. That is, data captured as a matter of course – typically for funding calculations, resource usage or disease monitoring. Repositories typically cited include HES in England or Patient Episode Data for Wales (PEDW). Having established that people with MS were willing to contribute data at scale it became important to check that a routine repository could support data related to multiple sclerosis queries. Access to the SAIL repository would allow me to see how MS was codified in routine data and as a consequence begin to understand patient flows and ultimately how to best make use of this unique source of data.

It is understood that routine data repositories are not ideal for rare diseases such as MS. They lack fine-grain detail such as current type of MS, or dates related to diagnosis. They can, however, be host to a huge amount of supplemental information that can enhance what data *is* present within the repository. Ultimately MS Register *would* be loaded and linked within SAIL, but this project was to make use of existing SAIL data and establish some exemplar analysis. This project could help contribute to the overall scientific body of knowledge about MS in the UK and in the process expand my understanding of what might be possible (and what limitations to expect) in later MSR linkage.

I identified that there was work needed around the role of Vitamin D in MS (Ascherio et al., 2010),(Ebers, 2008). and also in looking at the environmental factors involved with MS and evidence around the month of birth effect (Dobson et al., 2013). These were topics which could feasibly be investigated using routine data. Moreover, questions around environment and conception are clearly of interest to people with MS themselves, as if found to be relevant to the development and progression of the disease, then there may be behavioural changes that could be recommended to mitigate risks.

Aim

In this paper I attempted to identify people with MS within the routine data contained within PEDW which contains 100% of inpatient and outpatient activity for Welsh hospitals. I looked for population-level indicators that could be used as a proxy for vitamin D absorption based on location and how this may apply to the perceived 'month of birth' effect.

My input

As the System Architect of the MS Register, I carried out the literature review of papers pertaining to nationwide coverage of MS incidence and worked out the details of the case-finding algorithm. I then set out secondary topics of interest that the data should cover in

order to see what evidence was present within Welsh routine data; specifically, the population to be analysed, the hints towards vitamin D exposure, and comment further on the 'month of birth' effect. As second author on this paper, I came up with the aims, reviewed the statistical methodologies, assisted in analysing and making sense of the results and was heavily involved with the editing and proofreading of the manuscript.

Method

To identify pwMS within PEDW I identified the ICD-10 code for acute demyelinating disease (G35) for case finding. This was then linked within SAIL with a Lower Super Output Area code – which is a less identifiable location parameter than a postcode. This allowed analysis of incidence within a specified area to examine proximity to coasts, and hence serve as a potential proxy for potential higher exposure to vitamin D, which was then further linked to Met Office data for amount of sunshine hours per Lower Super Output Area (LSOA).

I defined the study period as only containing valid birth dates after 1938, and used Chi-Square tests to compare the births of our cohort of people with MS against the UK population from Office of National Statistics (ONS) data. For location data, I aggregated MS cases by LSOA over the study period to create the dependent variable. Substantive predictors were hours of sunshine per day, latitude, longitude, and whether the LSOA was a coastal city. I explored various interactions among predictors and used the pseudo-R squared statistic as a criterion for selecting the best model.

Results

The average annual incidence rate per 100,000 people in Wales was 9.10 (95% CI 8.80,9.40). These data looked robust by age group – though using in/outpatient data to find cases in a rare disease is problematic, as if there were no hospital admissions then they would not appear in the data. This would also account for the increase in incidence in the 85+ category as older patients are more likely to have a hospital admission. The data did bear out the month of birth effect in MS as I observed an increased birth effect for those born in April compared to the UK population (Observed to Expected Ratio: 1.21 (95% CI: 1.08, 1.36)) as compared with the general population (Chi-Sq = 10.99, df = 1, $p < .001$).

The main finding, that Wales has an incidence rate similar to Scotland, was important additional information in determining the effect of environment on MS. More than this, however, I had generated an initial algorithm to reliably identify MS cases within Wales and to link them with diverse datasets. This would be useful for future studies and effectively demonstrated the utility of linked data.

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RESEARCH ARTICLE

Sunshine, Sea, and Season of Birth: MS Incidence in Wales

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Data Availability Statement: A minimal dataset containing geographical information (LSOA, long-lats, population counts broken down by age group, sex, and year, sunshine levels, coastal indicator) is included as a supplementary file. Individual-level data for MS patients is accessible by applying to the SAIL Databank (http://www.saildatabank.com/) after approval by the Swansea University Institutional Ethics Board for researchers who meet the criteria for access to confidential data. Researchers who require access to the data may contact Ms.Cynthia McNerney (c.l.mcnerney@swansea.ac.uk), Information Governance Coordinator) in the first

Abstract

Maternal sun exposure in gestation and throughout the lifetime is necessary for vitamin D synthesis, and living near the sea is a population level index of seafood consumption. The aim of this study was to estimate the incidence rate of multiple sclerosis (MS) in Wales and examine its association with sun exposure, coastal living, and latitude. The study used a database of MS hospital visits and admissions in Wales between 2002 and 2013. For the 1,909 lower layer super output areas (LSOAs) in Wales, coastal status, population, longitude/latitude, and average sunshine hours per day were obtained. Age-specific and age-standardised MS incidence were calculated and modelled using Poisson regression. The distribution of births by month was compared between MS cases and the combined England and Wales population. There were 3,557 new MS cases between 2002 and 2013, with an average annual incidence of 8.14 (95% CI: 7.69–8.59) among males and 12.97 (95% CI: 12.44–13.50) among females per 100,000 population. The female-to-male ratio was 1.86:1. For both sexes combined, the average annual incidence rate was 9.10 (95% CI: 8.80–9.40). All figures are age-standardized to the 1976 European standard population. Compared to the combined England and Wales population, more people with MS were born in April, observed-to-expected ratio: 1.21 (95% CI: 1.08–1.36). MS incidence varied directly with latitude and inversely with sunshine hours. Proximity to the coast was associated with lower MS incidence only in easterly areas. This study shows that MS incidence rate in Wales is comparable to the rate in Scotland and is associated with environmental factors that probably represent levels of vitamin D.

Introduction

Several non-genetic factors including Epstein-Barr virus, insufficient sun exposure, and smoking are reported to increase the risk for multiple sclerosis [1]. With the UK having one of the highest prevalence rates for MS in Europe, [2]it is important to refine and update the incidence rate of this degenerative disease. Scotland has a prevalence rate (255 per 10^5)[2]that is higher than the rates both in England (199.9 per 10^5) and Wales (168 per 10^5)[3]. Relatively few

instance. A request made in writing will be reviewed by the Information Governance Review Panel and if approved, data access will be provided.

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studies reported age- and sex-specific incidence rates [3, 4]and we are unaware of a study covering the entire Welsh nation.

It is theorised that the variation in MS prevalence by geography is due to environmental factors acting on genetic predispositions [5]. Vitamin D obtained from sunlight and the diet is converted by the body into the metabolite 1,25-dyhydroxyvitamin D which activates the vitamin D receptor (VDR) in cells [6]. In the brain, 1,25-dihydroxyvitamin D has direct and indirect effects on T-cell lymphocytes, modulating the immune system's inflammatory response [7].With sufficient vitamin D, the balance between T-helper lymphocytes type 1 and type 2 is stabilized. By contrast, vitamin D deficiency is associated with having more disease-causing T-cells at the expense of regulatory cells [8]. This process is shared with other autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, and lupus erythematosus [9, 10].

Although the effects of sun exposure, latitude and month of birth overlap, month of birth is an index of vitamin D availability in gestation [11]while latitude probably reflects life-long exposure to UV radiation [12]. Sun exposure is the primary source of vitamin D synthesis in humans and its relevance to MS is well-studied. The critical periods for sunshine exposure have been variously reported as infancy and early years [12]to the entire childhood and adolescence [13]. Immigration from a low to a high risk area before age 15 (but not after) was associated with higher MS risk [14].

According to a systematic review, 16 studies found an excess of MS births in April or spring. In England and Scotland, MS births were higher in April or May than in the rest of the year, compared to the general population [10]. With vitamin D deficiency as the hypothesized cause of higher MS birth rates in spring, it is surprising that no association of 25OHD levels and risk of multiple sclerosis was found [15]. Using a Mendelian randomization method, Mokry and colleagues [16]reported that alleles associated with decreased 25OHD increased the odds of MS, indicating that vitamin D insufficiency is probably a causal agent for MS. Overall, the preponderance of evidence, a dose-response relationship, and biological plausibility all support a causal interpretation [6].

The correlation of MS prevalence with latitude is well-replicated. Studies from the US, Japan, and Australia/New Zealand reported that greater distance from the equator correlated with higher numbers of cases [17, 18]. The most striking effect is seen in temperate Tasmania where MS prevalence is seven times higher than in tropical northern Queensland [19]. By contrast, the "latitude gradient" was not observed in Norway and in France [20] and a SW-NE gradient was reported in the latter [21]. Latitude probably reflects levels of UV and vitamin D. It could however be confounded by the genetic similarity of people living in the same place [3]. One way of teasing apart genes and environment is by accounting for the distribution of the HLA-DRB1 allelle (the main genetic component for MS) when mapping MS prevalence by latitude. Simpson and colleagues reported that the association of MS with latitude persists after controlling for HLA-DRB1[22].

The influence of dietary vitamin D insufficiency or supplementation on MS is less widely studied. Circumstantial evidence from Norway showed a lower incidence of MS in coastal fishing areas as compared with inland areas [23]. It is proposed that a diet rich in fatty seafood augments UV levels [20]in the winter. However, seafood and dietary sources are not deemed adequate to meet the optimal 25OHD serum level of 75 nmol/l level [24]. A review of clinical trials reported that high-dose vitamin D supplementation was not associated with a decreased relapse rate for MS patients [25].

Our objectives in this study were to estimate age and sex specific incidence of MS in Wales and to assess its relation with sunshine hours, latitude, living by the coast, and month of birth.

Materials and Methods

Data sources

The data for this project were collated from various sources. Data on MS episodes came from the Secure Anonymised Information Linkage (SAIL) Databank, an electronic repository of health data hosted by Swansea University [26, 27]. SAIL aims to take advantage of routinely collected person-level electronic data for health and social research. SAIL was queried for persons having an ICD code of 340 or G35x (MS) during the period 2002 to 2013. Using ICD codes for case ascertainment has a sensitivity between 85–92.4 and a specificity between 55.9–92.6 [28]. The Patient Episode Database for Wales (PEDW) database in SAIL has 100 percent coverage of inpatient and outpatient (daycase) hospital visits in Wales. Since the UK clinical guidelines of 2003 [29]have required that MS diagnosis be made by a specialist neurologist on the basis of lesions, the PEDW is a trustworthy source of confirmed MS cases. PEDW does not capture MS cases diagnosed in primary care. PEDW has individual-level data, obscuring the values of certain variables (e.g. date of birth becomes week of birth) for confidentiality. Each person has a unique identifier (called an "anonymous linking field") which matches one-to-one with a valid NHS number [30]. We extracted from PEDW the gender, week of birth, and Lower Layer Super Output Area of residence (LSOA) of patients with MS. In the UK, an LSOA is a geographic area with a mean population of 1,500. There are 1,909 LSOAs in Wales.

Mid-year population estimates from 2002 to 2013 for all LSOAs in Wales were downloaded from the Small Area Population Estimates of the ONS website. We summed these age-and -gender-specific mid-year estimates in order to estimate the person-years contributed by each LSOA. This served as our denominator for calculating incidence rate.

The UK Office of National Statistics (ONS) also has a list of LSOAs designated as coastal communities (n = 422, for Wales). Accordingly, we coded all LSOAs in this list as "1" and the rest as "0". There were LSOAs that changed (either merged or split) between the UK Census 2001 and 2011 so we harmonized the codes using a cross-reference file provided by the ONS.

For sunshine levels, we used the 30-year average sunshine hours per day at each LSOA for the period 1961 to 1990. The Met Office does not provide sunshine levels for each LSOA. Instead, the Met Office divides UK land area into 440 grid boxes, each measuring 25 square kilometres [31]. The method for constructing these grids is described elsewhere [32]. These grid boxes are associated with rotated longitude/latitude values which we translated into real longitude/latitude using a reference table at this web page: http://ukclimateprojections-ui.metoffice.gov.uk/ui/docs/grids/prob_land_25km_rotated/index.php. Also, ONS has a file that indicates the population centroids (in longitude/latitude) for each LSOA. We then matched each population-weighted LSOA to the appropriate grid box based on the shortest haversine distance. Unlike Euclidean distance, haversine takes into account the earth's curvature. In summary, the MET Office provided sunshine hours for grid boxes which we matched to LSOAs provided by the ONS using the longitude/latitude as the merge field.

Statistical Analysis

We calculated age-standardized incidence by first creating five-year age groups and dividing the number of cases by the corresponding person-years in each LSOA. We collapsed the first two groups (0 to 10 years) due to small numbers of cases. Age-specific estimates were calculated separately for males and females. We finally standardized these rates to the 1976 European standard population. Age-standardization allows for the comparison of rates where the age structure of populations are not the same.

To examine whether MS is seasonal by birth, we compared the number of MS patients born in any given month with their counterparts in the general population of England and Wales. Because month of birth was not tallied separately by the UK Office of National Statistics (ONS) until the 1960s, we had to use combined figures for both nations. Furthermore, the ONS only started recording month of birth from 1938. As a result, our month of birth analysis was restricted to 2,927 MS patients (82 percent) who were born since 1938. We performed chi-square tests to test whether the pattern of MS births resembled the general population. To keep the family-wise error rate at .05, we required that each month's chi-squared result be significant at an alpha of .004.

We examined the influence of the environment by aggregating MS cases per LSOA (if any) over the study period. This was our dependent variable. Our substantive predictors were hours of sunshine per day, latitude, longitude, and whether the LSOA was a coastal city. For ease of interpretation, we centred latitudes on Aberystwyth (latitude = 52.42) in the north/south dimension. We also centred longitudes on Carmarthenshire (longitude = -4.26) in the east/west dimension. Mid-year population estimates were used as an offset term in order to relate the number of MS cases per LSOA with its mid-year population for each year. We explored various interactions among predictors and used the pseudo-R squared statistic as a criterion for selecting the best model.

Results

From 2002 to 2013, there were 1,256 new MS cases among men and 2,301 new cases among women. The average annual incidence rate per 100,000 people was 8.14 (95% CI: 7.69–8.59) for males and 12.97 (12.44–13.50) for females, for a sex ratio of 1.86:1 (female: male). For the total population, the combined average incidence rate was 9.10 (8.80–9.40) (Table 1).These

Table 1. Average Annual Incidence of Multiple Sclerosis in Wales, by Sex and Age Group, from 2002 to 2013.

	Males			Females			Combined		
Age Group	New Cases	Person-Years	Age-specific rate**	New Cases	Person-Years	Age-specific rate**	New Cases	Person-Years	Age-specific rate**
0 to 9	9	2,092,636	0.43	8	1,985,087	0.4	17	4,077,723	0.42
10–14	19	1,139,767	1.67	11	1,083,276	1.02	30	2,223,043	1.35
15–19	25	1,209,624	2.07	26	1,155,986	2.25	51	2,365,610	2.16
20–24	32	1,208,228	2.65	60	1,177,370	5.1	92	2,385,598	3.86
25–29	46	1,052,498	4.37	117	1,045,740	11.19	163	2,098,238	7.77
30–34	75	1,056,610	7.1	158	1,084,615	14.57	233	2,141,225	10.88
35–39	116	1,162,755	9.98	272	1,209,146	22.5	388	2,371,901	16.36
40–44	109	1,251,252	8.71	282	1,302,072	21.66	391	2,553,324	15.31
45–49	124	1,215,787	10.2	290	1,260,590	23.01	414	2,476,377	16.72
50–54	116	1,156,919	10.03	244	1,194,131	20.43	360	2,351,050	15.31
55–59	133	1,158,074	11.48	192	1,192,054	16.11	325	2,350,128	13.83
60–64	98	1,088,416	9	155	1,123,714	13.79	253	2,212,130	11.44
65–69	86	918,417	9.36	120	966,922	12.41	206	1,885,339	10.93
70–74	76	737,121	10.31	94	826,237	11.38	170	1,563,358	10.87
75–79	49	567,655	8.63	83	715,409	11.6	132	1,283,064	10.29
80–84	44	378,833	11.61	47	577,891	8.13	91	956,724	9.51
85+	99	250,076	39.59	142	569,334	24.94	241	819,410	29.41

** Per 100,000 population

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figures are standardized to the age-distribution of the 1976 European population. The mean age at first hospital admission for males was 52.95 (SD: 19.94) years and 50.47 (SD: 18.32) for women. As expected, MS incidence in ages 0 to 10 for both sexes is low. In males, there is an increase starting around age 30 and around age 25 for females. For both sexes, the highest incidence is at age-group 85 and above, but this could be due to the aggregation of many ages or late diagnosis. The disease onset is likely to have occurred much earlier—we address this matter in the limitations section. See Table 1 for the sex-specific and combined MS incidence estimates. The distribution of cases and sunshine levels by LSOA (Fig 1).

Month-by-month chi-square tests showed a 21 percent higher number of MS births in April (Observed to Expected Ratio: 1.21 (95% CI: 1.08–1.36)) as compared with the general population ($\chi^2 = 10.99$, df = 1, $p < .001$). No other month had birth numbers that differed significantly from expected (Table 2). The regression model for the count of MS cases by LSOA showed that MS incidence decreased by 25 percent for each additional hour of sunshine per day. For each additional latitude north of Aberystwyth, MS incidence increased by 37 percent. There was a significant *Coast* × *Longitude* interaction indicating that easterly coastal areas in

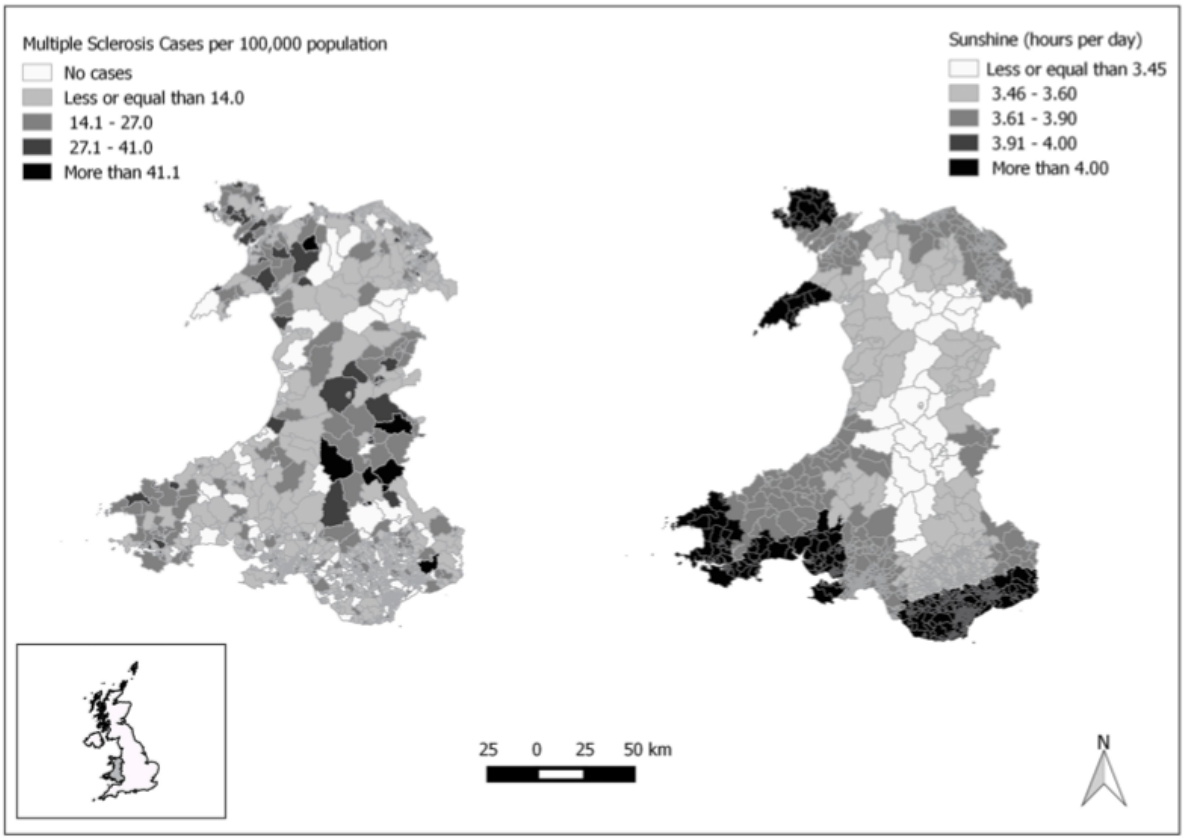

Fig 1. Average annual incidence of MS (2002 to 2013) and Average Sunshine Hours per day in Wales, UK. Left panel: Incidence by LSOA. Right panel: Sunshine hours per day from 1961–1990. Inset: Wales location within the UK.

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Table 2. Month of birth from 1938 to 2005, General Population vs People with MS in Wales.

Month	All England and Wales births	Births of People with MS in Wales		Observed-to-Expected Ratio (95% CI)	Chi-square	P
		Observed	Expected			
January	3,938,576	238	244	0.98 (0.86–1.11)	0.15	0.70
February	3,693,432	221	229	0.97 (0.84–1.10)	0.28	0.60
March	4,162,616	230	258	0.89 (0.78–1.01)	3.04	0.08
April	3,973,205	298	246	1.21 (1.08–1.36)	10.99	<.001
May	4,146,640	268	257	1.04 (0.92–1.18)	0.47	0.49
June	3,969,042	242	246	0.98 (0.86–1.12)	0.07	0.80
July	4,062,277	254	252	1.01 (0.89–1.14)	0.02	0.90
August	3,953,452	244	245	1.00 (0.88–1.13)	0.00	0.95
September	3,942,578	265	245	1.08 (0.96–1.22)	1.63	0.20
October	3,882,108	228	241	0.95 (0.83–1.08)	0.70	0.40
November	3,664,537	220	227	0.97 (0.85–1.11)	0.22	0.64
December	3,802,065	219	236	0.93 (0.81–1.06)	1.22	0.27

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Wales had lower MS incidence. For those living west of Carmarthenshire, living in a coastal area did not make a difference in incidence rates (Table 3 and Fig 2).

Discussion

The main finding of this study is that Wales has an incidence rate of MS similar to that of Scotland. Higher daily sunshine hours was inversely associated with MS. Our results also supported the latitude hypothesis, with the number of cases increasing as one moves north within Wales itself. Residing in a coastal area was associated with lower MS incidence in more easterly areas. There was a higher than expected number of MS births for April, suggesting that maternal sunshine exposure during pregnancy is involved.

In comparison to other studies, our all-Wales age-standardized incidence rates are considerably higher than in previous UK studies [4, 33]where the estimates for females ranged from 7.2 to 11.52 and for males 3.1 to 4.84 per year per 10^5 population [3, 34]. A previous study of average annual MS incidence in South East Wales during 1985 to 2005 reported 1.65 and 4.66 for males and females, respectively per 10^5 population. Various areas in Scotland have reported combined sexes incidence rates of 5.7 in Glasgow, 7.2 in Tayside, 10.1 in the Border Region, and 12.2 in the Lothian Region per year per 10^5 population [34–36]. It is striking that our sex-specific incidence rates for Wales are within the same range as the estimates for Scotland. Our incidence rates for Wales are slightly higher than for those in France where the figures are 7.5 for males and 10.4 for females [37]. Although the latter is consistent with the latitude gradient, the similarity of the incidence rates in Wales and Scotland is quite unexpected.

Table 3. Quasi-poisson regression model of MS births by LSOA Characteristic.

Explanatory Variable	Incidence Rate Ratio	95% CI
Average daily sunshine hours	0.75	0.63–0.91
Latitudes north of Aberystwyth	1.37	1.30–1.45
Longitudes east of Carmarthenshire	0.74	0.68–0.81
Coastal area (yes/no)	0.94	0.83–1.05
Longitudes east of Carmartenshire x Coastal Area	0.61	0.49–0.77

doi:10.1371/journal.pone.0155181.t003

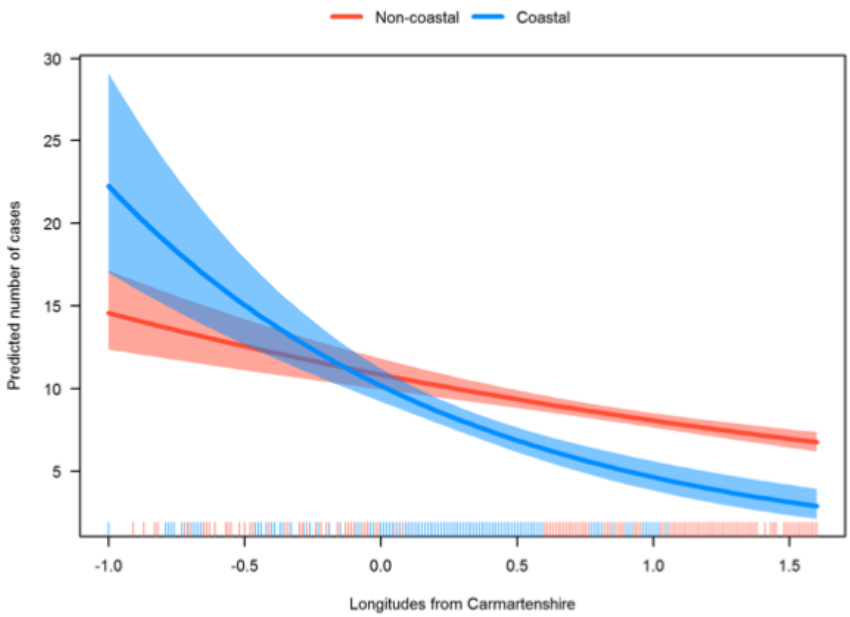

Fig 2. Coast × Longitude interaction in the incidence of multiple sclerosis by LSOA in Wales, UK. Rug plot on the x-axis indicates the distribution of coastal and non-coastal areas.

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That the highest numbers of MS cases for both males and females occurred in the 85 and over age group is surprising. This could be an artefact of the higher hospital visits in this sub-group and/or collapsing more than five age groups in the category. One possibility is that although MS was pre-existing in some of these older people, a diagnosis was made only upon visiting the hospital—which tends to be more likely at older ages. The change in UK guidelines in 2003 may have contributed to the high MS incidence in the 85 and above age group. The other possibility is that there truly is a spike in MS incidence in these ages during 1990 to 2010 [3]. Unfortunately, we cannot determine which of the two possibilities is true.

The finding that MS cases are 20 percent higher in April has been previously reported in Scotland, the UK as a whole, Italy, and Finland [11, 38]. However, contrary to previous results, we neither found higher births in May or lower births in October or November[10, 39]. Dobson and colleagues proposed that month of birth reflects the availability of vitamin D in the prenatal environment [11]. Vitamin D helps tune the foetal immune system by suppressing inflammatory cytokines and promoting self-tolerance [7]. MS represents a disturbance of the immune system in which T-cells attack myelin protein [40].The winter months in the UK are from December to February, so those born in April would have been in their 5^{th} to 7^{th} months of gestation. It would be important to further examine if maternal vitamin D sufficiency is more critical in certain months of gestation.

Above 52 degrees latitude (roughly, Cambridge or Aberystwyth, UK), there is insufficient UV light for vitamin D synthesis during the winter months [29]. In this regard, proposals have been put forward for dietary supplementation [11]. The ecological nature of our study design makes us unable to interpret the link of more easterly coastal residence with lower MS births. A future study, with measures of individual fish consumption, would be able to comment on this

finding. The evidence regarding dietary supplementation is inconsistent. Eating fish three times a week or more in childhood and adolescence was found protective for MS [30]. Munger and colleagues [41]pooled two large prospective cohorts of nurses (n > 150,000). They found that >400 IU of vitamin D from supplements was protective for MS. In Canada, the association of serum 25OHD levels and dietary vitamin D intake (from milk and multivitamins) was studied [42]. No significant association was found. More studies are required as to whether the risks of fortifying food with vitamin D are outweighed by its benefits. Thus far, small clinical studies have shown that vitamin D supplementation is safe and these results support large randomized trials [6].

As with all studies, the present one is subject to several limitations. First and foremost, the present study is ecological in design and did not include individual level variables other than week of birth and gender. While coastal residence could serve as population-level proxy for seafood consumption, the lack of person-level dietary information precludes an interpretation. Secondly, the present study relied on a hospital-based register. This means that persons with MS who do not visit the hospital go undetected. We have chosen to err on the side of underestimation by not using the general practice register for two reasons. UK clinical guidelines since 2003 require that patients suspected of having MS be referred to a specialist neurologist on the basis of CNS lesions [29]. Furthermore, a previous study using the general practice database noted that the diagnosis of multiple sclerosis in the General Practice Research Database has not been validated [3]. In analysing MS months of birth, we used the combined England and Wales births from 1938 to 2005. This could affect our estimate of April births if the birth pattern differed between England and Wales. The main strengths of our study are data from a hospital-based administrative register with 100 percent coverage of hospital visits in Wales and data on sunshine hours at the small area level.

Conclusion

This is the first study of MS incidence covering all of Wales and we found an incidence rate comparable to that of Scotland. The variation in incidence is related to geographical factors that probably represent levels of vitamin D.

Supporting Information

S1 File. Minimal Data to Replicate the Analysis. This is a compressed Microsoft Excel file containing lower layer super output areas in Wales, population counts by age and gender groups, sunshine levels, and an indicator for coastal status.
(DOCX)

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Author Contributions

Conceived and designed the experiments: LDB RMM KTD. Analyzed the data: LDB TP. Contributed reagents/materials/analysis tools: RMM KTD TP KEW GJN. Wrote the paper: LDB RMM KTD TP KEW GJN.

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Conclusions

This paper served a number of purposes within the creation of a working MS Register:

1. There was utility in the data stored within routine datasets; this data *would* be enhanced when Register data was sufficiently comprehensive to be imported and linked to.
2. Many estimates of multiple sclerosis incidence are based on cohort studies rather than population-based ones. Typically, incidence in MS is measured in cases per 100,000 per year and is frequently stratified by gender as there is increasing incidence in women. The data below is all for female gender. A study using the Clinical Practice Research Database (CPRD), involving 4 million people from English and Welsh GP practices in 2007 reported female MS incidence of 7.2 per 100,000 per year (95% CI: 6.5, 7.8) (Alonso et al., 2007). A study carried out in South East Wales identified an increasing incidence from 2.65 to 7.30 (per 100,000) between 1985 to 2007 (Hirst et al., 2008). Our finding from the entire Welsh population of female incidence of 8.14 (95% CI: 7.69, 8.59) was therefore very much in line with these earlier cohort studies and illustrated the utility of the algorithm for case finding.

The paper also began to expand what could be possible with reference to the routine data source – eliciting an initial algorithm for case finding based on the index date of the population (2002-2013) and the presence within PEDW of a G35 code. Another crucial element regarding linkage, established in this paper, was the introduction of geography to the analysis. The use of LSOA codes as a proxy for location data was essential in this paper for calculating vitamin D exposure when linked to a diverse dataset (Met Office). This proof would be essential for all manner of later analysis; one example is a later study using MSR data to link deprivation and access to Disease Modifying Therapies (Das et al., 2022).

As stated in the paper, a limitation of this approach was to ignore the population of pwMS contained within general practice. Though a confirmed diagnosis of MS can only be given by a hospital-based consultant neurologist, these entries would not be entered into a GP record without that confirmation having occurred. At this point in SAIL's evolution, the percentage of the Welsh GP population covered in SAIL was less than 80%. This limitation also highlights how important it is to begin to truly understand the population that you are working with. For

example, it is known that acute MS patients in North Wales are actually treated in England (at the Walton Centre, in Liverpool). This data would therefore not appear within Welsh hospital data.

Over and above the findings of the paper itself, this work demonstrated to MS researchers at large the diverse nature of the SAIL databank and its utility to MS research. This was important to the funders of the MS Register and would also lay the groundwork for later linkage of MS Register data within the SAIL databank.

Chapter 5: Validating the portal population of the UK MS Register

I had now demonstrated that the portal of the UK MS Register could reliably capture relevant PRO information from pwMS and that there was utility in using data linkage in routine data repositories such as SAIL. This could be used for case-finding algorithms and for carrying out useful research into areas such as disease incidence and Vitamin D.

I next looked at how to build the reputation of the Register amongst clinicians and academics so that it could become more widely known as a respected and valuable research tool. In order to do this, it was necessary to validate the portal population of the UKMSR against the clinical population.

Background

The most common argument from clinicians and other MS researchers questioning the concept of the MS Register, specifically regarding the portal population, was "how do you know that they actually have MS?"

Informed consent is an essential component of ethical research. In order to participate in the portal element of the UKMSR, participants must read and agree to a ‘terms of service’ stating the registers position on data storage and use of data. They confirm that they are aged over 18, resident in the UK and have a neurologist confirmed diagnosis of MS. Clinically, there is a process of informed consent where an appropriately eligible patient is identified by the clinical team, given a consent pack and then appropriate time to consider the information before proceeding with consent. After consenting participants are given a unique study identifier (studyID). This studyID could then be entered onto the portal and provide a deterministic match against the clinical data received from an NHS site. Additionally, probabilistic matching (Sayers et al., 2016) could be carried out, linking participants that may not have entered their studyID. Probabilistic matching is particularly important in a population that can be potentially treated at multiple sites as this leads to the possibility of duplicated consent. Probabilistic matching allowed for the identification of participants based on a number of demographic items, including surname, forename, date of birth, NHS number and postcode. The ability to do this formed an important part of the justification for seeking identity markers in the application to the Ethics Committee at the outset of the UK MS Register.

Using these matching methods would allow us to link those patients that were consented at a site and online. This linkage of the clinical population with the online one would provide the evidence needed that the online population – even those that did not have consent at a clinical site – did indeed have MS.

My input

For this paper I wrote the initial draft, and carried out the data extraction, cleansing and analysis. Data were collected via the Register. I carried out all of the primary edits based on responses from other authors and submitted them to the journal. I responded to these

comments and edited the manuscript in accordance with reviewer feedback.

Aim

To validate that the portal population of the UK MS Register is a representative cohort of patients with multiple sclerosis.

Methods

Data were collected from NHS sites and people with MS as described elsewhere in this document. I carried out data cleansing. For the clinical population, this primarily involved removing invalid and incorrect dates (191 out of 3,194). For the portal population, I did the same, whilst also removing a number of participants that had died (we were informed by relatives) or who had entered impossible demographic criteria. It is worth stating again that a pragmatic design choice for the portal population at the outset was to not enforce mandatory fields on all aspects as this was causing a large amount of cognitive load on people with MS who were trying to complete the forms. For example, the requirement to have an 'exact' diagnosis date, in the form DD/MM/YYYY, potentially up to 20 years after diagnosis, could be unduly stressful. As a consequence of this, although data completeness was high, there was a small number of obviously incorrect dates – such as diagnosis before onset, or onset before date of birth. As a pragmatic approach, dates of diagnosis were reduced to just years of diagnosis for the analysis and any unlikely events were excluded. Later iterations of the Register portal would reduce these incidents happening and we would establish a dialogue with participants to get them to check their responses at intervals. Data cleansing left 11,021 valid records from portal participants.

Following this, I analysed the data using the R language with simple descriptive statistics and standard deviations. A two-sample Kolmogorov-Smirnov (K-S) test was then implemented using age at diagnosis and current age. This is a non-parametric statistical test which determines if two different continuous variables are from the same distribution.

Results

There were 11,021 portal participants with sufficient data for analysis and 3,003 clinical cases. Given the disparity between numbers of available clinical sites (24 at this stage) and all portal users, only 676 individuals were linked between the datasets. Table 1 shows the comparison of the datasets.

Table 1: UKMSR datasets compared by age, age at diagnosis and MS type at diagnosis

	Clinical	Portal	Linked
n	3,003	11,021	676
Mean age (std-dev)	48.8 (±11.9)	52.6 (±11.7)	48.3 (±11.3)
Mean age at diagnosis (std-dev)	37.4 (±10.6)	39.3 (±10.2)	38.6 (±10.6)
Female gender (%)	2,178 (75.2)	8,052 (73.1)	493 (72.9)
PPMS (%)	198 (6.5)	1,514 (13.7)	51 (7.5)
RRMS (%)	2,564 (85.3)	7,408 (67.2)	567 (83.8)
SPMS (%)	122 (4.0)	839 (7.6)	21 (3.1)
Other (%)	119 (3.9)	1,260 (11.4)	37 (5.4)

The overall demographics of the population reflected results from other disease registers: that is, an increased ratio of female to male patients (2.7:1) with a higher percentage of patients with Relapsing Remitting disease – notably more so in the clinical population, given that patients receiving treatment are most likely to attend clinic. This percentage falls in the portal population with more people with SPMS appearing, the Register proving an outlet into which people who have no treatment options (at that time) were able to contribute to research. The mean age at diagnosis is in line with what has been reported in some other MS datasets (Celius and Smestad, 2009) and slightly older than is being currently reported globally (Walton et al., 2020).

Using the K-S test to compare the portal and clinical data for current age and age at diagnosis ($D = 0.078$, $p < .001$) shows that there is very little difference between the populations – though the null hypothesis is rejected. Other sub-analysis carried out against different populations, for example, just comparing the Relapsing populations led to a closer fit ($D = 0.131$, $p < .001$) but again they are drawn from slightly different populations.

The results were statistically close enough to justify that the portal population of the UKMSR was a population of people with MS.

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Conclusions

This paper was crucial in illustrating that the portal population and the clinical cohort could be linked, and that they behaved like a cohort of people with confirmed multiple sclerosis. Although the numbers linked from both populations were relatively small (676) it was enough to carry out appropriate statistical testing to demonstrate that the cohorts were similar at the level of statistical significance. A limitation that should have been acknowledged in the paper at the time, was due to the relatively small amount of linked data that could be obtained; the comparative analysis only used phenotype and ages of diagnosis and onset with participant age. A more contemporaneous approach would account for many more variables - particularly around disability outcomes.

It is an interesting observation of the UK MS Register that I have always been defensive of 'low' numbers within cohorts – particularly of the linked cohort at this stage of the Register's development; taking a clinical population of 3,194 and a portal population of 14,720 and only identifying 676 individuals between them (<5%) felt low. However, it is worth viewing this in context: the biggest international MS Register (NARCOMS) validates their cohort as having confirmed MS in 52 of their 17,601 'active' participants (Marrie et al., 2007). Moreover, many MS clinical trials make use of numbers of participants significantly less than this: MS Stat2 has 408 participants (Chataway et al., 2014), while CHARIOT has 200 (Queen Mary University of London, 2022).

This study, therefore, was enough to demonstrate the case to the satisfaction of most UK neurologists. It also illustrated the scale of the cohorts *beyond* that that was linked: the portal

and the clinical populations taken separately were amongst the largest routine data collections in MS in the UK, and larger than many MS populations in the world. This paper illustrated the data collection methodologies that were in place at UK MS specialist treatment centres (and how fragmented these were), and published the pro-forma for the minimum dataset that was actively being collected as part of the UK MS Register's effort to improve MS data collection in the UK. This could serve as a flag to other MS databases that were being established at the same time, including TONIC (Young et al., 2022) and OPTIMISE (Dobson et al., 2021). We demonstrated that no matter what overall data was being collected within the UK, a common minimum dataset was desirable. This would prevent duplication, make potential data sharing easier, and ensure that there was a standard for the collection of MS data in the UK – as up until now this had been an extremely fragmented space.

This was an important paper for the MS Register. The ability to justify, through publication and peer review, that the MS Register populations were validated, was vital for the ongoing usefulness of the Register. This gave us, and the researchers that were beginning to work with the MS Register, the ability to reference one article that would answer the most repetitive – though necessary – question from peer reviewers about the composition and validity of the platform. This publication represents a first step in the continual and overall validation of the Register; the linked and clinical populations were relatively small at this point and have subsequently increased to many more thousands, with corresponding increased data quality. However, data from the MS Register portal population is now published in high impact factor journals (Brain and Neurology) and data from *all* populations of the UKMSR has been part of international data linkage efforts that have formed part of European and American studies (Salter et al., 2020), (Simpson-Yap et al., 2021)

Having carried out this validation, my next step was to demonstrate how the Register could serve as a backbone for the collection of more diverse datasets (outside of the ones that had been utilised up thus far), whilst still fulfilling the ambition to meet the requirements of people with MS and their clinicians.

Chapter 6: A rapid electronic cognitive assessment measure for multiple sclerosis: validation of Cognitive Reaction, an electronic version of the Symbol Digit Modalities Test

Background

I had identified from the outset that the MS Register should be capable of linking 'other' datasets as part of its day-to-day operations. An element of this had been addressed in Chapter 5, illustrating the utility of routine data within the SAIL databank. However, the ability to create an entirely new dataset that could have immediate impact as part of routine clinical care, and that could help people with MS assess the effect of the disease beyond the mobility, disability and quality of life metrics that the UKMSR had collected so far, was important.

The collection of timely and accurate cognitive data in people with MS is a significant issue. Although there are a plethora of different tests available, many of them require the presence of a clinician or technician to manage the test and advise the participant. The testing itself can be demanding for patients who may already have significant cognitive impairments and can be fatigued with the demands of attending an appointment. Although the UKMSR had a large battery of outcome measures, there was no reliable electronic cognitive test that was quick to administer. I therefore developed, released, and validated an electronic variant of the Symbol Digit Modalities Test (SDMT) for iPad devices, called CoRe (Cognitive Reaction test), with the intention that it could be taken by patients in 90 seconds. The paper SDMT is a proven measure in MS Clinical trials and the more 'routine' collection of cognitive data into the UKMSR would illustrate the flexible nature of the Register to collect diverse datasets.

Aim

To design, develop, release, and test an electronic measure suitable for rapidly assessing cognition in people with MS.

My input

I carried out the research and literature review in order to establish the most suitable test for adaptation to electronic form. I then developed and deployed the application and participated in the initial testing with people with MS on the application in a number of settings. The initial draft of the paper was written by me, with analysis contributed by MS Register researchers and clinical oversight on results from the Register's lead neurologist. Once the draft was fit for publication, I submitted it to a journal, responded to reviewers and made edits where necessary

Method

Having made the initial decision to write an SDMT application, Apple platforms were targeted as the most suitable environment to use. Portal data indicated that Apple devices were the most popular in use, the language for development (Swift) was more familiar to me than others, and the experience of using the devices was most consistent for considerations such as screen response time and precise symbol layout on the screen. Once the app had been developed, it was necessary to carry out robust testing of the application in people with a variety of MS types, on a range of treatment options, and of differing ages to ensure that the application was suitable. The most obvious test route was to compare the results of the CoRe test with the results of the paper SDMT. We established that we would also need a 'healthy' cohort of non-MS patients to compare against. This would ensure that any deviations from the paper test could be present in both populations.

The validation study for the CoRe test captured pwMS in both clinical and non-clinical settings and followed up where possible after one month. A cohort of healthy volunteers were also recruited to assess the test's responsiveness in a healthy population. Table 2 shows the demographics of the populations tested by the CoRe application.

For patients tested in clinical and non-clinical settings, the paper SDMT was administered with an operator present in the traditional way. CoRe testing was carried out immediately afterwards to minimise any chance of bias. Those tested in clinic (DMT patients returning for infusions) were retested one month later.

Table 2 : Demographics of cohort and healthy Controls undertaking the CoRe test. The UKMSR population included for comparison.

Characteristic	Total UKMSR[a]	CoRe[b] cohort (MS[c])	CoRe cohort (healthy controls)	Cohort difference[d], chi-square test (*df*)	Cohort difference[d], *t* test (*df*)	*P* value
Total participants, n	11,387	102	45	N/A[e]	N/A	N/A
Gender, n (%)				0.3 (1)	N/A	.57
Female	8387 (73.7)	70 (68.6)	28 (62.2)			
Male	3000 (26.3)	32 (31.4)	17 (37.8)			
MS type, n (%)				N/A	N/A	N/A
RRMS[f]	5988 (52.6)	86 (83.2)	N/A			
PPMS[g]	1492 (13.1)	5 (5.6)	N/A			
SPMS[h]	2945 (25.9)	9 (9.3)	N/A			
Other	962 (8.4)	2 (1.9)	N/A			
Age (years), mean (SD)	53.6 (11.8)	44.0 (11.0)	38.1 (11.9)	N/A	2.891 (145)	.004
Age at diagnosis (years), mean (SD)	39.2 (10.3)	34.6 (10.6)	N/A	N/A	N/A	N/A
EDSS[i], median (range)	6 (0-9.5)	3.5 (1-8)	N/A	N/A	N/A	N/A

UKMSR : UKMS Register, CoRe : Cognitive Reaction, RRMS : Relapsing Remitting Multiple Sclerosis, PPMS : Primary Progressive Multiple Sclerosis, SPMS : Secondary Progressive Multiple Sclerosis

Results

A number of statistical tests were carried out to compare the responses of pwMS against the paper test and against the healthy population, namely Shapiro-Wilks, Paired-T and Pitman-Morgan, all showing a high level of agreement between tests. Retesting those participants at one month on the CoRe showed high inter-test reliability with an intraclass correlation coefficient (ICC) of 0.94 (95% CI: 0.88, 0.97; $F_{29,30}$=33.2; p < .001). Figure 4 illustrates the ICC.

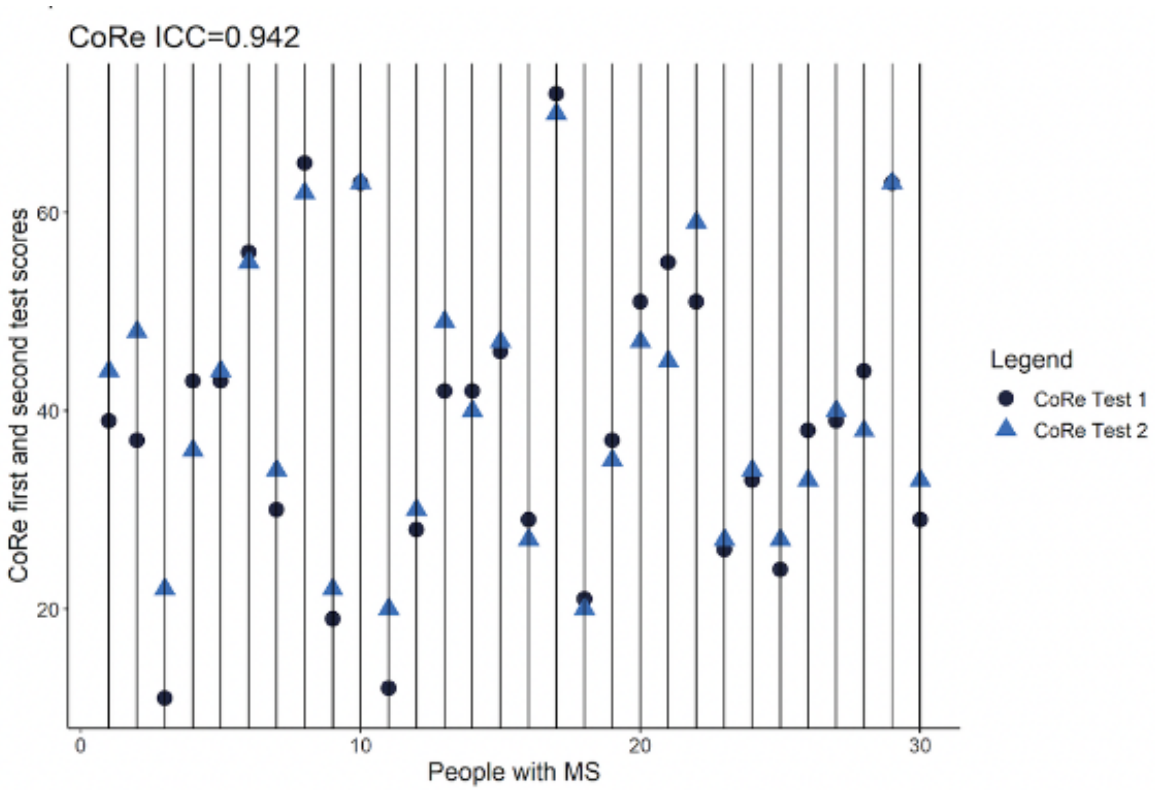

Figure 4 : Intraclass Correlation Coefficients between the first and re-tested CoRe Tests

We carried out further tests (Analysis of Variance (ANOVA), Tukey) looking at the effect of age and disability on the CoRe instrument and found that older, more disabled participants performed worse in CoRe testing than in the paper test. A novel outcome of this test, not seen in other SDMT based tests, was our ability to monitor speed of response across the tests. This 'speed of reaction' result takes the 90-second duration of the test and splits it into three 30-second sub tests. This method highlighted a noticeable difference in performance during the test. Healthy controls and people with MS were observed to respond more quickly over the duration of the test, with the healthy cohort responding even more quickly throughout all periods of the test. Multivariate analysis on the results (R^2=0.396; $F_{5,3973}$ =520.4; p <.001) showing that female gender in both controls and pwMS showed some slowing of reaction time over the duration of the test but increasing disability was a more significant factor.

In conclusion we designed, developed, and implemented a novel cognitive test to

participants of the MS Register population and validated its effectiveness as an outcome measure.

Paper 5: A rapid electronic cognitive assessment measure for multiple sclerosis: validation of Cognitive Reaction, an electronic version of the Symbol Digit Modalities Test

Original Paper

A Rapid Electronic Cognitive Assessment Measure for Multiple Sclerosis: Validation of Cognitive Reaction, an Electronic Version of the Symbol Digit Modalities Test

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Abstract

Background: Incorporating cognitive testing into routine clinical practice is a challenge in multiple sclerosis (MS), given the wide spectrum of both cognitive and physical impairments people can have and the time that testing requires. Shortened paper and verbal assessments predominate but still are not used routinely. Computer-based tests are becoming more widespread; however, changes in how a paper test is implemented can impact what exactly is being assessed in an individual. The Symbol Digit Modalities Test (SDMT) is one validated test that forms part of the cognitive batteries used in MS and has some computer-based versions. We developed a tablet-based SDMT variant that has the potential to be ultimately deployed to patients' own devices.

Objective: This paper aims to develop, validate, and deploy a computer-based SDMT variant, the Cognition Reaction (CoRe) test, that can reliably replicate the characteristics of the paper-based SDMT.

Methods: We carried out analysis using Pearson and intraclass correlations, as well as a Bland-Altman comparison, to examine consistency between the SDMT and CoRe tests and for test-retest reliability. The SDMT and CoRe tests were evaluated for sensitivity to disability levels and age. A novel metric in CoRe was found: question answering velocity could be calculated. This was evaluated in relation to disability levels and age for people with MS and compared with a group of healthy control volunteers.

Results: SDMT and CoRe test scores were highly correlated and consistent with 1-month retest values. Lower scores were seen in patients with higher age and some effect was seen with increasing disability. There was no learning effect evident. Question answering velocity demonstrated a small increase in speed over the 90-second duration of the test in people with MS and healthy controls.

Conclusions: This study validates a computer-based alternative to the SDMT that can be used in clinics and beyond. It enables accurate recording of elements of cognition relevant in MS but offers additional metrics that may offer further value to clinicians and people with MS.

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KEYWORDS

cognition; multiple sclerosis; eHealth; electronic assessment; patient reported outcomes; neurology

Introduction

Background

Multiple sclerosis (MS) is an inflammatory demyelinating and degenerative disease of the central nervous system and the most common nontraumatic cause of disability in young adults worldwide [1]. The dominant phenotype is characterized by relapses (attacks) and remissions, known as relapsing-remitting MS (RRMS). In the majority of those affected with RRMS, the condition evolves, within 10 to 15 years, into secondary progressive MS (SPMS). About 15% of people with MS develop primary progressive MS (PPMS), characterized by progressive neurological dysfunction from onset [2].

Motor impairment forms the most overt impact of MS but cognitive impairment affects up to 40% of people with MS, rising to 80% in those with the progressive forms of the disease [3]. It has substantial impact on disability and can, when present in isolation, limit employment prospects [4]. However, in the early stages of MS, formal cognitive testing can show minimal changes in a wide variety of domains [5]. Later, as the disease advances, the picture becomes more coherent, with impairments in speed of information processing, attention, episodic memory, and executive function dominating. These impact independence and mood and can lead to social isolation [6].

Cognitive testing itself can be demanding on patients, causing difficulties for those with attentional disorders, fatigue, and physical limitations [7]. The time and attention required in a busy clinic environment makes test delivery in a routine context a challenge for both patient and assessors. To this end, in MS, a number of simplified tests of cognition have been developed for clinical use. These include the Brief International Cognitive Assessment for MS [8], the Brief Repeatable Battery of Neuropsychological Tests [9], and the Minimal Assessment of Cognitive Function in Multiple Sclerosis [10]. In most cases, these tests are still largely paper- or apparatus-based exercises completed in front of an assessor and take the form of a battery of tests that incorporate multiple testing methodologies.

One common element of the MS testing batteries is the Symbol Digit Modalities Test (SDMT) [11]. It assesses organic cerebral dysfunction and has a proven history as an effective outcome measure in a number of MS trials [10,11] and in other conditions [12]. The SDMT consists of matching symbols against digits within 90 seconds, the result being the total number of correct answers. Participants are given a practice number of attempts and then perform the timed assessment. The implementation of the test typically takes 5 minutes, including instruction and demonstration. The responses can be written or spoken out loud and recorded by the assessor [13].

A number of electronic variants of the SDMT have been developed [14,15], but as yet, they are not used routinely to assess cognitive impairment [16]. Their implementation varies from the original paper test, but the impact of these slight variations is as yet unclear, as impairment in individuals with MS can vary widely with different elements, such as fatigue, which can slow reactions, and physical issues such as ataxia or weakness, which can introduce further variability if a screen or keyboard needs to be manipulated. This is a further challenge if a test is to be administered without an assessor present. However, the computer-based approaches have the potential to offer additional information over the paper-based or oral approaches, as additional metrics can be quantified and these may enhance the information available from the test.

The United Kingdom Multiple Sclerosis Register (UKMSR) was established in 2011 as a means of capturing real-world evidence of living with MS in the United Kingdom. There are comprehensive data on 11,387 people with MS registered on the UKMSR via the internet and more than 13,000 consented clinically via a network of National Health Service (NHS) centers [17]. An online portal facilitates collection of longitudinal patient-reported outcomes (PROs) and real-world evidence of living with MS, but none of the instruments currently capture cognitive function. Given the need to understand in more depth the performance characteristics of electronic testing and the key role of cognitive impairment in MS, we developed an electronic variant of the SDMT that could be implemented rapidly and routinely at clinical centers to address this need. Ultimately, as an electronic register, if this type of testing is validated, then it could be also carried out in the patient's home, which would also help patients who are unable to physically attend clinics.

Objectives

This paper aims to develop, validate, and deploy a computer-based SDMT variant, the Cognition Reaction (CoRe) test, that can reliably replicate the characteristics of the paper-based SDMT and assess its utility for deployment as a meaningful measure to assess cognition in an MS population.

Methods

Population

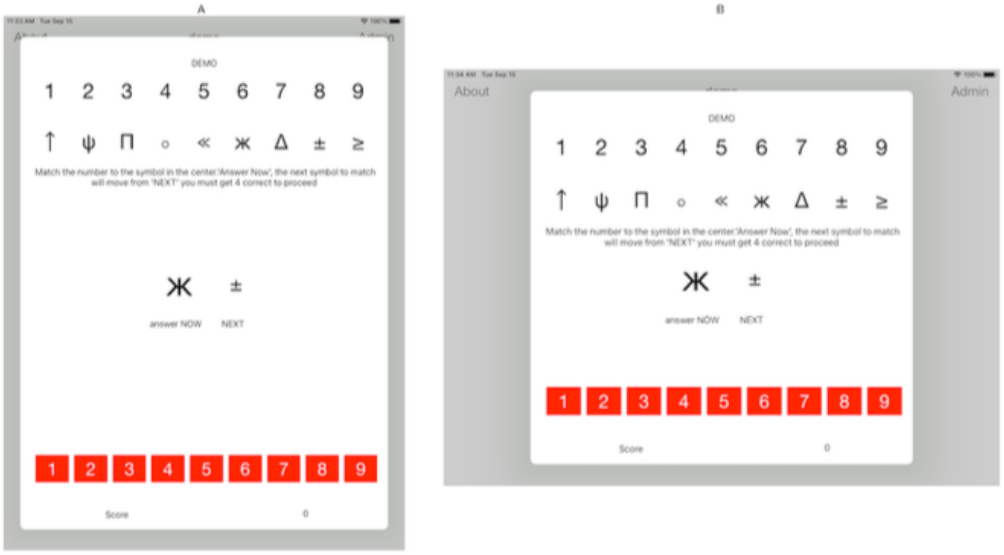
All participants gave informed consent, and the study has ethical approval from South West Central Bristol Ethics Committee (16/SW/0194). Participants were recruited from Morriston Hospital, Swansea Bay University Health Board and Charing Cross Hospital, Imperial College Healthcare NHS Trust. The people with MS that took part in the study were recruited at either progressive MS teaching days or as part of their routine visits to their respective hospitals. Demographic data and an Expanded Disability Status Score (EDSS) [18] were recorded at the time of testing. Healthy volunteers were recruited from Swansea University Medical School and Imperial College London to provide a control group of test scores with anonymized demographic data. Healthy volunteers were recruited from among the staff at the two clinical sites and included a mix of staff and PhD students from Swansea University. None of the healthy controls had MS and no one approached refused. All participants had completed at least full

formal secondary education. There were no declared visual problems in the population.

CoRe Test App

The Cognition Reaction (CoRe) test was inspired by the SDMT; however, there are some key differences. The CoRe test presents 9 different symbols displayed at the top of the screen, with corresponding numbers, 1 through 9, underneath. The symbols are randomized every time the app is launched, and the center of the screen displays 2 symbols, the one to be identified now and the next one. At the bottom of the screen, there are a number of buttons labelled 1 through 9 that participants tap to match the central symbol on the screen. Data recorded include the number of symbols accurately tapped, as for the SDMT, but in addition, CoRe automatically registers the time between responses and the number of incorrect responses. Further details of the app are presented in Multimedia Appendix 1 [19,20]. The app is entirely self-contained, with no requirement for internet access. The CoRe test app can be seen in Figure 1.

Figure 1. Cognitive Reaction test app shown running in portrait and landscape modes.



App Testing

For the MS population, participants first completed the paper SDMT using the traditional written method, requiring the paper test, a pen, and a stopwatch. Following this, participants were handed an iPad and given an introduction by a researcher from the UKMSR team, merely demonstrating the 2 orientations that the device could be placed in. The orientation that participants chose was not recorded as part of this assessment. They were then invited to follow the written directions on the app. They were first presented with a demonstration mode and encouraged to run through at least once. A score of 4, which was displayed on the screen, was required to progress to the main test. This could be repeated if desired. Once ready, participants hit "start" and were given 90 seconds to complete the test. A countdown timer was displayed on the screen of the iPad. Visual acuity was not formally assessed, and no participants claimed that they could not see the icons on the tablet screen. Test environments were controlled for noise and disturbance. Some participants were retested 1 month later in the same environment to determine the consistency of the results.

Statistical Analysis

Analysis was carried out using the Pandas library for Python (version 3.773) [21] and the R statistical language (version 3.6.0; R Foundation for Statistical Computing) [22]. Graphs and images were generated using Seaborn [23] and ggplot2 (version 3.0.0) [24]. Correlation was used to compare the validity of the paper and electronic versions of the tests and the test-retest reliability of the CoRe test. Pearson r was calculated for test scores from the CoRe test and the SDMT, with mean difference evaluated using a 2-tailed paired samples t test and differences in variances compared using a Pitman-Morgan test for paired samples. Intraclass correlation was also performed on the first and second CoRe and SDMT test results. A Bland-Altman analysis was used as an additional measure of equivalency. The sensitivity of the CoRe and SDMT scores to disability levels and age were measured using analysis of variance (ANOVA) statistics, with post hoc Tukey tests used to determine any significant differences between groups.

To utilize the additional data generated by the CoRe test, the question answering velocity (QAV) was quantified as a measure of cognitive function. This was defined as the total number of correct answers given at a time divided by total current time elapsed in the test (correct answers/seconds). Multivariate linear regression was performed to determine if any relationship existed between the QAV and the time period of the questionnaire. The CoRe test lasts a total of 90 seconds, and responses were divided into thirds to study the rates of change over the first, second, and third sections of responses for each patient. For analysis, EDSS scores were divided into 3 categories: low (EDSS of 0-2.5), medium (EDSS of 3-5.5), and

high (EDSS of 6-10), as was age, with categories of 18-34 years, 35-54 years, and >55 years.

Results

Demographics

A total of 102 people with MS were recruited to the study (Table 1), of whom 30 returned within 1 month for a repeat test. All patients were over 18 years of age and had no significant comorbidities that would exclude them from being able to complete the paper or CoRe tests. No participants were excluded from the study, and none reported a relapse of MS at any point in the testing. Mean age of the people with MS cohort tested was younger than the overall MS Register population, with a slightly lower proportion of patients with PPMS and SPMS (Table 1). A total of 45 anonymous healthy controls were tested during the development of the app; apart from not completing an initial paper SDMT, conditions were similar to the MS cohort. Both healthy controls and people with MS had completed at least 12 years of education.

Table 1. Demographics of cohort and healthy controls undertaking the CoRe test. The UKMSR population is shown for comparison.

Characteristic	Total UKMSR[a]	CoRe[b] cohort (MS[c])	CoRe cohort (healthy controls)	Cohort difference[d], chi-square test (*df*)	Cohort difference[d], *t* test (*df*)	*P* value
Total participants, n	11,387	102	45	N/A[e]	N/A	N/A
Gender, n (%)				0.3 (1)	N/A	.57
Female	8387 (73.7)	70 (68.6)	28 (62.2)			
Male	3000 (26.3)	32 (31.4)	17 (37.8)			
MS type, n (%)				N/A	N/A	N/A
RRMS[f]	5988 (52.6)	86 (83.2)	N/A			
PPMS[g]	1492 (13.1)	5 (5.6)	N/A			
SPMS[h]	2945 (25.9)	9 (9.3)	N/A			
Other	962 (8.4)	2 (1.9)	N/A			
Age (years), mean (SD)	53.6 (11.8)	44.0 (11.0)	38.1 (11.9)	N/A	2.891 (145)	.004
Age at diagnosis (years), mean (SD)	39.2 (10.3)	34.6 (10.6)	N/A	N/A	N/A	N/A
EDSS[i], median (range)	6 (0-9.5)	3.5 (1-8)	N/A	N/A	N/A	N/A

[a]UKMSR: United Kingdom Multiple Sclerosis Register.

[b]CoRe: Cognitive Reaction.

[c]MS: multiple sclerosis.

[d]Difference between people with multiple sclerosis and healthy controls.

[e]N/A: not applicable.

[f]RRMS: relapsing-remitting multiple sclerosis.

[g]PPMS: primary progressive multiple sclerosis.

[h]SPMS: secondary progressive multiple sclerosis.

[i]EDSS: Expanded Disability Status Score.

CoRe Test in People With MS and Control Group: Comparison of Total Correct Responses

The first set of CoRe test scores for people with MS were compared with those of the healthy control group. Mean test results for people with MS were 39.0 (SD 13.3), while mean scores for the healthy control group were 56.1 (SD 15.9). An unpaired *t* test found that people with MS had significantly lower scores (t_{145}=–6.769; *P*<.001), with no significant difference in variance between the groups ($F_{101,44}$=0.701; *P*=.15).

CoRe Test and SDMT in People With MS: Comparison of Total Correct Responses

People with MS completed both the CoRe test and SDMT together on 2 occasions, 1 month apart. The first test response distributions for the CoRe test and SDMT were normally distributed (Shapiro-Wilk tests with *P*=.48 and *P*=.61, respectively) and were strongly correlated (Pearson r_{100}=0.800; *P*<.001). First test participants scored a mean of 4.40 responses lower for the CoRe test compared with the SDMT, as seen in Table 2 (paired samples t_{101}=5.390; *P*<.001), but there was no significant difference in the variance (Pitman-Morgan test: t_{100}=–0.879; *P*=.38), with good agreement between tests (Figure 2). When the CoRe test and SDMT were repeated for a second time, the mean CoRe test score was not significantly lower than

the SDMT (1.4 responses difference; t_{29}=0.954; P=.35). Again, there was a strong correlation between the second CoRe test and second SDMT (Pearson r_{28}=0.842; P<.001). Table 2 shows the baseline and retest responses for those who completed it.

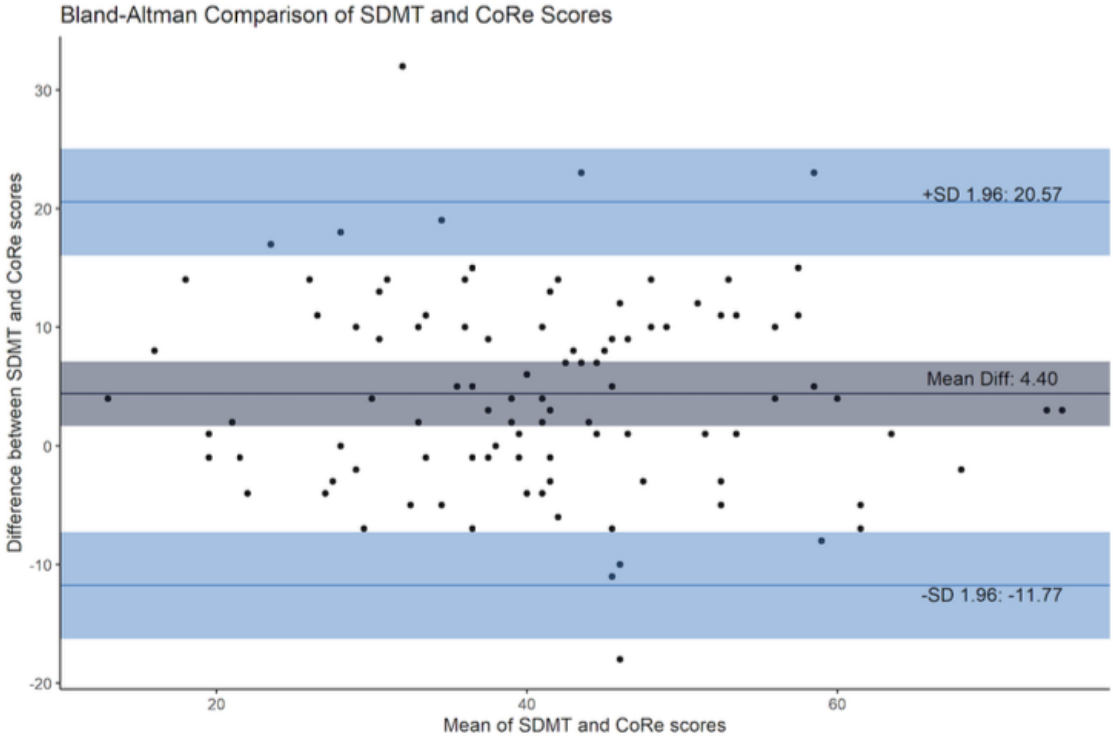
Table 2. Baseline and retest SDMT and CoRe test total responses at baseline and retest 1 month later.

Test	Participants, n	Score, mean (SD), range
Baseline		
SDMT[a]	102	43.4 (12.6), 15-76
CoRe[b] test	102	39.0 (13.3), 11-73
Retest		
SDMT	30	41.9 (14.6), 14-76
CoRe test	30	40.5 (13.9), 20-70

[a]SDMT: Symbol Digit Modalities Test.

[b]CoRe: Cognitive Reaction.

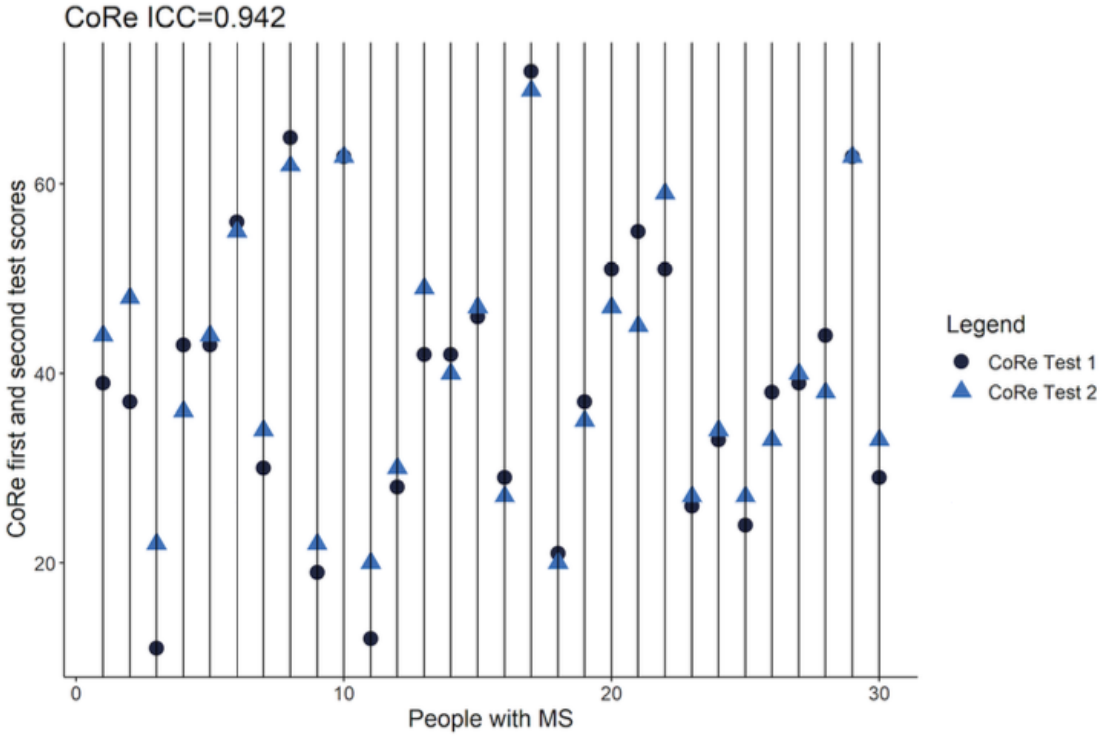
Figure 2. Bland-Altman comparison of first CoRe test with paper SDMT scores. CoRe: Cognitive Reaction; SDMT: Symbol Digit Modalities Test.



CoRe Test and SDMT Test-Retest Reliability

First and second CoRe test and SDMT scores were evaluated for test-retest reliability and scores at a 1-month interval. The CoRe tests were normally distributed and demonstrated consistency (Pearson correlation coefficient r=0.947; t_{28}=15.60; P<.001). Differences in means were normal (Shapiro-Wilk test P=.81) and not significantly different (t_{29}=–0.944; P=.35), with equal variances (Pitman-Morgan t_{28}=1.784; P=.09). The intraclass correlation coefficient between the first and second CoRe tests was found to be 0.942 (95% CI 0.882-0.0972; $F_{29,30}$=33.2; P<.001) (Figure 3).

Figure 3. Intraclass correlation coefficients between the first and retested CoRe tests. CoRe: Cognitive Reaction; ICC: intraclass correlation coefficient; MS: multiple sclerosis.



Test-retest correlations were observed in the same people completing the SDMT at a 1-month interval. Scores were normally distributed and consistent (Pearson correlation r=0.936; t_{28}=14.052; P<.001) and differences in means were normal (Shapiro-Wilk test P=.44) and not significantly different (t_{29}=–0.919; P=.37), with equal variances (Pitman-Morgan t_{28}=–0.743; P=.46). The intraclass correlation coefficient between the first and second SDMT tests was found to be 0.935 (95% CI 0.869-0.968; $F_{29,30}$=29.6; P<.001).

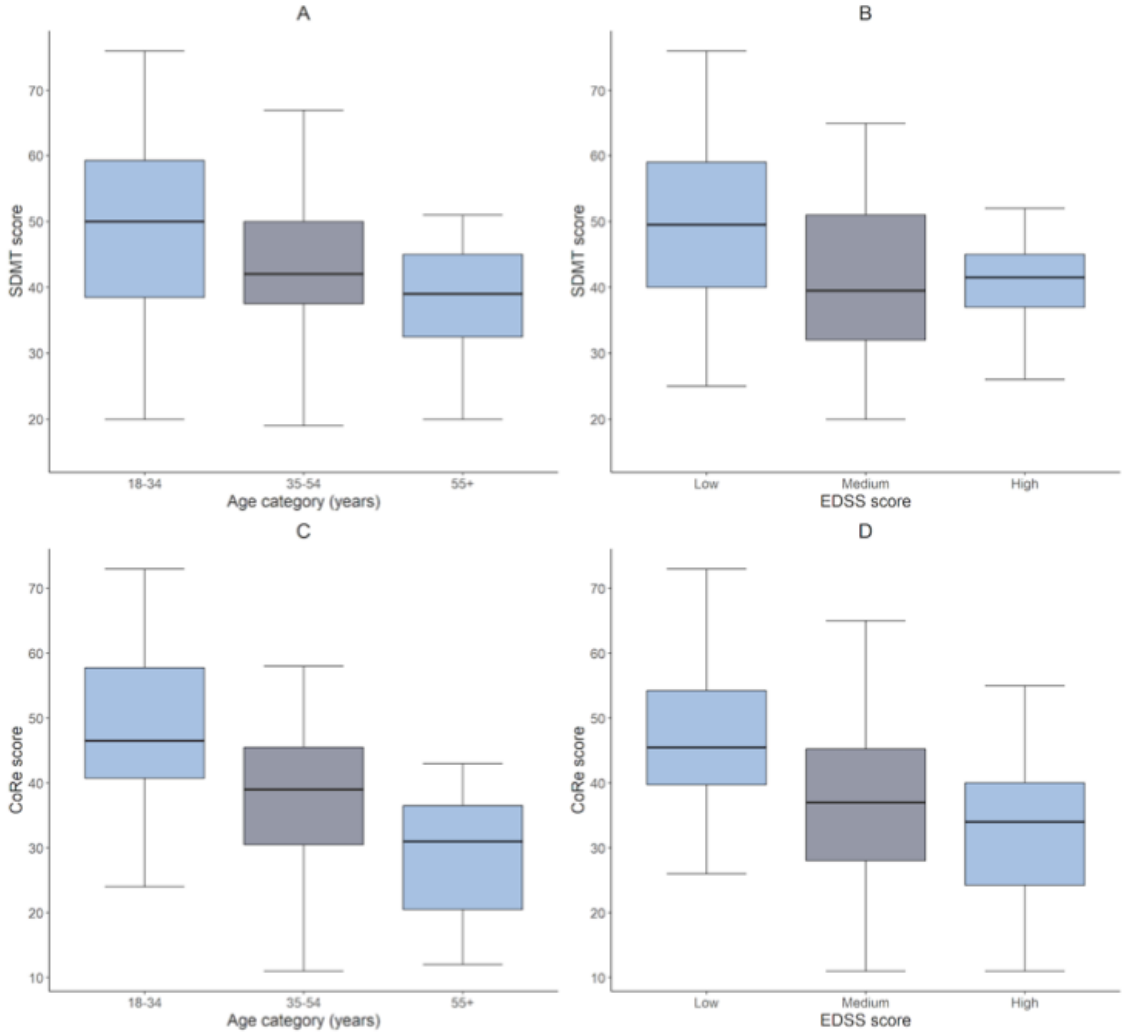
CoRe Test Total Correct Response Score Is Impacted by Age and Disability in MS, Whereas SDMT Is Only Affected by Disability

We examined the impact of age, gender, and EDSS on the total correct responses (Figure 4). An ANOVA for SDMT scores with respect to age and EDSS found no significant impact of age (aged 18-34 years: mean 48.1, SD 15.5; aged 35-54 years: mean 43.2, SD 11.8; and 55+ years: mean 38.3, SD 9.0; F_2=1.036; P=.36), but significance for EDSS (low EDSS: mean 49.8, SD 12.9; medium EDSS: mean 41.4, SD 12.3; high EDSS: mean 38.6, SD 9.8; F_2=8.574; P<.001); post hoc Tukey tests showed higher scores in those in the lowest EDSS category compared with those in the highest EDSS category (P<.001) and compared with the medium EDSS category (P=.01). No significant difference was found between the low and medium EDSS categories.

In contrast, an ANOVA for CoRe test scores showed a significant difference in the total responses with age (aged 18-34 years: mean 48.6, SD 13.5; aged 35-54 years: mean 38.3, SD 11.6; and >55 years: mean 28.9, SD 9.8; F_2=8.633; P<.001) and EDSS (low EDSS: mean 47.4, SD 11.6; medium EDSS: mean 36.8, SD 12.7; high EDSS: mean 32.1, SD 10.7; F_2=18.151; P<.001). Post hoc Tukey tests showed those in the age group of 18 to 34 years had significantly higher scores than those in the 34 to 54 years (P=.01) and 55+ years group (P=.001), with no difference between the medium and high age groups. The lowest EDSS category was associated with higher CoRe test scores than both other groups (P<.001), with no difference between the medium and high EDSS groups.

Gender was not found to be significant for either SDMT or CoRe test scores.

Figure 4. Mean SDMT and CoRe scores with age categories and EDSS scores. CoRe: Cognitive Reaction; EDSS: Expanded Disability Status Score; SDMT: Symbol Digit Modalities Test.



Speed of Reaction (Question Answering Velocity) Derived From the CoRe Test Increases Throughout the Test and Correlates With Age, Gender, and Disability

Due to the way data are acquired for the CoRe test, we were able to measure the speed of reaction to each question and calculate the QAV as correct answers over time elapsed (seconds) continuously throughout the assessment. There was a significant range of QAV over the time frame of the test in people with MS, as illustrated in Figure 5, which shows the two individuals with the lowest and highest scores in the CoRe test. Breaking down the total correct answers into 3 sections also allowed us to quantify the change in QAV over the course of the CoRe test. Multiple linear regression models with the variables age, gender, and EDSS in people with MS found that QAV increased in each third of the test in people with MS and healthy controls (Table 3).

Figure 5. A polynomial regression of QAV for those people with MS with the lowest and highest scores in the cohort. CoRe: Cognitive Reaction; EDSS: Expanded Disability Status Score; MS: multiple sclerosis; QAV: question answering velocity.

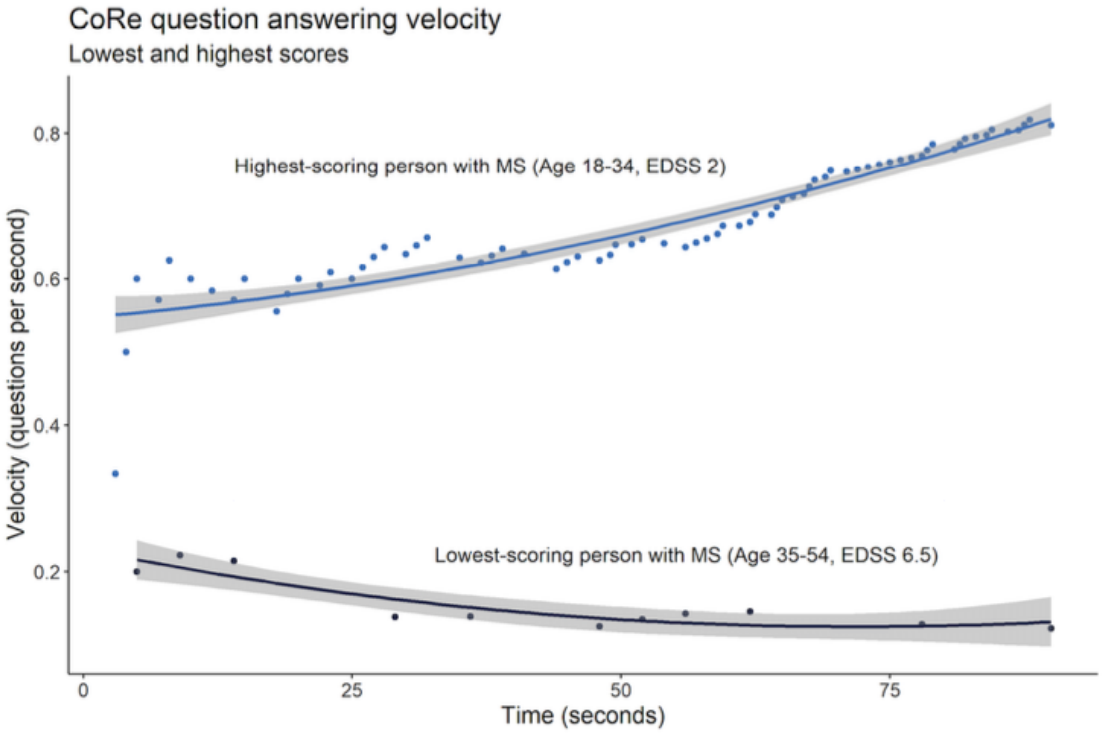


Table 3. Multivariate models in people with MS (R^2=0.396; $F_{5,3973}$=520.4; P<.001) and healthy controls (R^2=0.323; $F_{4,2521}$=300.1; P<.001) for QAV over the time frame of the Cognitive Reaction test, with additional covariates age and gender. EDSS scores are given for people with MS only.

Variable	QAV[a] of people with MS[b]		QAV of healthy controls	
	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value
Second section compared to first	.045 (0.037 to 0.053)	<.001	.070 (0.056 to 0.085)	<.001
Third section compared to first	.071 (0.063 to 0.080)	<.001	.110 (0.094 to 0.123)	<.001
Age	–.005 (–0.005 to –0.006)	<.001	–.008 (–0.007 to –0.008)	<.001
Female gender	.049 (0.041 to 0.056)	<.001	–.043 (–0.055 to –0.031)	<.001
EDSS[c]	–.017 (–0.015 to –0.019)	<.001	N/A[d]	N/A

[a]QAV: question answering velocity.

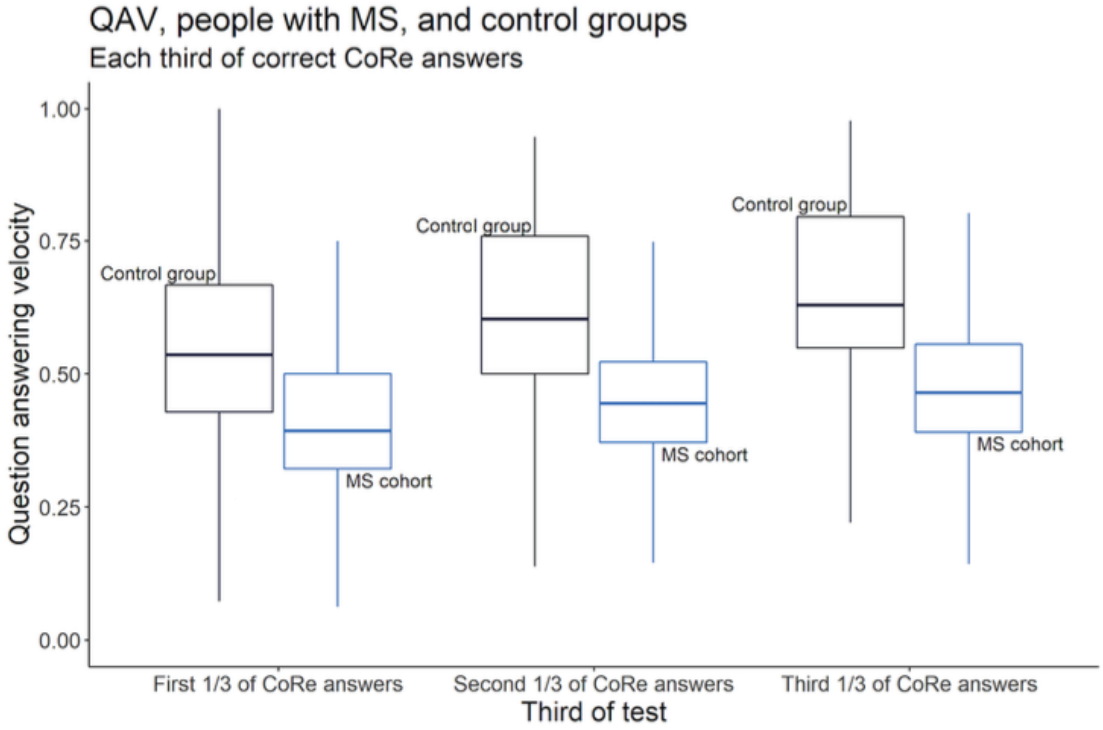
[b]MS: multiple sclerosis.

[c]EDSS: Expanded Disability Status Score.

[d]N/A: not applicable.

Both groups answered more quickly as the test progressed (the control group at an even faster rate than people with MS), with the second and third sections of their correct answers being completed in less time than the first. The gradient is similar in both populations (Figure 6). In both populations, increased age was associated with slowing of QAV by 0.007 to 0.008 questions per second for each year increase in age. For control participants, female gender was associated with a slowing of QAV by 0.034 questions per second, whereas in people with MS, female gender was associated with an increase in QAV of 0.049 questions per second. However, disability slowed QAV by 0.017 questions per second for every increase in EDSS by 1 point (Table 3).

Figure 6. Comparison of increase in speed between each test third for healthy and MS populations. CoRe: Cognitive Reaction; MS: multiple sclerosis; QAV: question answering velocity.



We next directly compared the variables associated with CoRe test QAV and the CoRe test total response score. A regression using the variables age, gender, and EDSS score found that the CoRe test QAV was significantly impacted by all 3 factors, whereas the CoRe test score (total correct answers) found significant impacts only from EDSS and age (Table 4).

Table 4. Impact of age, gender, and EDSS on total response score (R^2=0.383; $F_{3,98}$=20.3; P<.001) in people with MS cohort.

Variable	CoRe[a] test score	
	β coefficient (95% CI)	*P* value
EDSS[b]	–2.103 (–3.390 to –0.808)	.002
Age	–.489 (–0.713 to –0.265)	<.001
Female gender	4.413 (–0.155 to 8.981)	.06

[a]CoRe: Cognitive Reaction.

[b]EDSS: Expanded Disability Status Score.

Discussion

Summary of Findings

This study aims to validate an electronic variant of the SDMT, comparing the CoRe test with the established paper-based SDMT within an MS cohort in 2 independent UK centers, examining its overall reliability and suitability. In addition, we quantified an additional metric that can be extracted from the electronic implementation. The total response scores for the CoRe test were on average lower than the SDMT but showed good correlation with the paper test, though there are clear differences in responses across age groups. Having the understanding that the CoRe performs similarly across these deviations allows it to be compared with the paper-based test, though it is not a like-for-like match. However, the consistency of the test and its utility remain clear. The CoRe test showed consistent responses over time and demonstrated similar test-retest properties to the SDMT, as with other electronic implementations [14]. These findings suggest that the CoRe test is an appropriate alternative to measure of cognitive ability as assessed by the SDMT.

We confirmed that a reduction in correct responses for both the SDMT and CoRe test correlates with increasing disability, but in addition, a reduction in correct responses correlates with increasing age in people with MS. Using the advantages of an electronic implementation, we were able to measure the QAV

and found that both people with MS and healthy controls increase their QAV throughout the test and also that in both groups, an increased QAV correlates with younger age and male gender. This implies these correlations are not associated with MS-specific cognitive decline. However, increased QAV is also associated with lower disability, only present in those with MS. In our testing, increasing age showed a reduction in correct responses over the test. This finding corresponds with other SDMT testing in populations [25], and there is evidence for older participants performing poorly over the duration of the test, with studies showing decreased reaction times (about 0.5 ms/year) [26] in simple reaction-style tests in older people. There is also the effect of older people's familiarity with tablet computers [27] that could have some impact on this. This will be investigated in future testing.

There are a number of computer-based variants of the SDMT, one of the first being the computerized Symbol Digit Modalities Test (c-SDMT) [14], which showed excellent sensitivity in 119 people with MS versus 38 healthy controls, with people with MS performing significantly worse than the healthy controls. Use of the c-SDMT has not become widespread, most likely due to the technology platform that it was developed on and the stringent test description (Windows PC, 19-inch screen with participant at 15 inches from the screen), making deployment challenging. A more recent implementation of a computer-based SDMT is the processing speed test (PST) [15], which was also tested against a healthy control population and forms one element of the Floodlight assessment tool [28]. The PST showed similar results as we have demonstrated and has shown high reliability when reproduced within Floodlight on patients' own devices. Small differences in implementation of the same paper-based test can impact what is being tested and need to be understood. The CoRe implementation requires the screen to be touched, which adds a visuospatial element to the assessment, and this will have an impact in some people with MS. It also presents 2 symbols in random order as opposed to a standard sheet of symbols; this change means that there is less likely to be a learning effect on retesting. A key issue with computer-based implementation is the impact of rapid hardware and software development, which results in a need to develop applications that can adapt to a changing environment. Another issue is the variety of devices, such as desktops, laptops, and smartphones, that are currently in use, especially if the test is to be performed without an assessor present. CoRe has been developed to run at multiple screen sizes and on different devices, with an interface—two symbols seen at a time—that is suited to a small screen. This will have to be tested separately.

Prior studies, and our results, show that data produced by electronic tests are consistent, repeatable, and have utility to clinicians, informing on a vital aspect of patient care [29]. The scores on both paper SDMT and the CoRe test fall with increasing disability. The CoRe test is more sensitive than the SDMT to age, with the SDMT being only affected in populations older than 55 years [27]. The electronic CoRe test allows greater analysis of this effect, demonstrating slower mean response times in higher ages and disability groups. There is some evidence that there may be a gender difference in cognitive tests [30], with males and females performing differently at various ages in different test types. Notably, this is seen with visual reaction times, and this would be consistent with the implementation of the test presented here. The fact that this extra variable of reaction time (QAV) can be measured as part of the CoRe test could have clinical or research utility in the future. Having additional quantifiable clinical measurement information via a simple-to-implement and rapid test could hopefully have some relevance to everyday clinical practice, research, and medication trials. Benedict et al [13] state that the current definition of "NEDA" (no evidence of disease activity) is predicated on largely physical outcome measures, but cognition is so fundamental to socialization, employment, and quality of life beyond pure health care that a prolonged measurement of cognitive aspects could add a compelling dimension to our understanding of disease activity.

Limitations

We identified some limitations with this study. First, there were few people with MS with progressive disease and advanced disability, and we did not have complete directly measured cognitive assessments. In addition, the population that took 1-month follow-up tests was limited, and we have only tested this on a single type of device here. The 1-month period chosen for retest represents the hospital visit pattern for some patients on a particular disease-modifying therapy. Differing retest periods should be tested in the future. Although testing was performed in the presence of a researcher, they had little or no input on the actual test itself—though this has been shown to not have effect on these types of tests [31]. We also did not consider the orientation of the device as having any effect. This could also be incorporated into future testing on other devices.

Given that the CoRe test is consistent and repeatable, we intend to test the app on other devices, including laptops and a variety of smartphones. This will facilitate completion of the test away from the clinic and will enable us to integrate the CoRe test into the range of PROs captured by the UKMSR. Additionally, this will allow us to carry out testing among participants with higher disability and more progressive disease at different intervals to ensure that the test maintains its reliability and repeatability. We recognize that the CoRe is not an exact replacement for SDMT. It is an entirely new test [32], but it is comparable and measurable compared with the SDMT.

Conclusion

The CoRe implementation of the SDMT test is reliable and correlates with the paper-based SDMT, while also offering the additional metric of patient reaction time (QAV). This will allow clinicians and researchers to capture important additional metrics in people with MS, and potentially in other diseases, quickly and reliably on existing tablet hardware.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

CoRe test Application Details.
[DOCX File , 14 KB-Multimedia Appendix 1]

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Abbreviations

ANOVA: analysis of variance
CoRe: Cognitive Reaction
c-SDMT: computerized Symbol Digit Modalities Test
EDSS: Expanded Disability Status Score
MS: multiple sclerosis
NHS: National Health Service
PPMS: primary progressive multiple sclerosis
PRO: patient-reported outcome
PST: processing speed test
QAV: question answering velocity
RRMS: relapsing-remitting multiple sclerosis
SDMT: Symbol Digit Modalities Test
SPMS: secondary progressive multiple sclerosis
UKMSR: United Kingdom Multiple Sclerosis Register

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Conclusions

The purpose of designing my own cognitive test for the MS Register was to serve a number of outcomes. Firstly, as stated in the introduction of this chapter, it would add another diverse element of data collection to the overall battery of outcomes that were already available within the MS Register platform and the linkage of a novel dataset to these could add depth to the existing tests. Secondly it identified an underutilised area of assessment in routine MS care and treatment, cognition, that was rarely captured at MS clinics due to its time consuming nature and the requirement to have staff on hand to administer the test. Thirdly, it was clear from movements within regulators such as the European Medicines Agency recommending the use of a cognitive test such as the SDMT in guidance documents (European Medicines Agency, 2019) for assessment of drug relabelling trials. Lastly, the development of an application that could potentially be distributed via the 'app-store' where people with MS could learn about and interact with the MS Register in a mode that was not purely web-based could form a new interaction for a version of the MS Register away from the purely web-based format. This was a longer term ambition.

The development of this application was carried out with people with MS and clinicians with a variety of prototypes being tested with people with MS and in a clinical setting to ensure that the trial application would be fit for purpose. The initial version showed many more symbols than the 'up next' that was eventually settled on as striking a good balance between the paper and a purely electronic version. The most significant advance, other than the time saving and consistent test metric that electronic testing can bring, was the ability to randomise the symbol set before starting the test. In clinical settings where pwMS complete SDMT tests, response sheets are normally photocopies of the original document given by the test distributor. Anecdotally, patients may attempt to memorise these in order to 'pass' the test. This is clearly not the goal of cognitive testing and can bias the results.

Another significant discovery was the finding of intra-test performance (Question Answering Velocity). It's unsurprising that as people became used to the test over the 90 seconds that

their performance improved, that this was more noticeable in the healthy cohort (even when adjusted for age) is perhaps less surprising. MS is a condition that explicitly affects and inhibits speed of information processing and memory, and this is consistently demonstrated in the CoRe test. Typically SDMT is scored in terms of total score (correct answers in 90 seconds) out of a maximum value of 110. Normative data is normally required in populations to discover what the norm is within that group. Large normative populations that have completed SDMT in multiple sclerosis are not available at scale, and indeed the data captured as part of the development of the CoRe instrument has gone on to form the normative data for assessment with the NEuRoMS Study, which aims to assess and provide cognitive rehabilitation for people with MS. The CoRe instrument is also a fundamental part of this study (Nair et al., 2022).

The ability to assess cognition rapidly, reliably and without the requirement for someone else to help deliver the test in a clinic could help cognitive assessment for pwMS become more routine. This could clearly benefit all the stakeholders involved in MS care and research. As the MS Register moves closer to being part of clinical trials, the ability to deploy and link to diverse and vital instruments of assessment demonstrates the fundamental flexibility of the platform and how it can serve a huge diversity of simultaneous needs.

Chapter 7: Can we improve the monitoring of people with multiple sclerosis using simple tools, data sharing, and patient engagement?

Background

As has been presented in Chapters 2 and 3 of this document, the opinions, expectations and needs of people with MS were essential to development, direction, and operation of the UK MS Register. Having been a working Register for seven years, it became important to ensure that the direction of travel continued to meet those expectations and that if new expectations had arisen, now that there *was* a register to compare against, these should also be accounted for.

There was also the need to help design an element of the Register that had not fully been addressed since the initial conceptual work on development, namely how best to present the PRO information that was being captured via the UKMSR back to both participants and their clinicians.

My input

This was a more qualitative approach to a research question within the UK MS Register. My role as second author was to prepare the UK MS Register to display the proposed functional changes and display feedback, lead the PPI group through these, and respond to questions about the instruments and their meaning. I assisted the primary author with the drafting of the manuscript and interpreting the results following the implementation of the changes recommended by the PPI group, before editing and proofreading the final manuscript.

Methods

The lack of data from people with MS that would allow their clinical teams to make decisions on how best to proceed with care had been highlighted as being a particular problem. The lack of sensitivity of some of the measures employed – particularly EDSS as being too simple a metric of disability – were of particular concern. Categorising patients using this and other outcome measures (such as MRI scans) could lead to patients being unfairly categorised both in routine care and within clinical trials. More than that, involving people with MS (along with clinicians and researchers) in the selection of what outcome measures to use as endpoints, and how this data could be presented, could lead to increased interaction from all stakeholders.

It was clear that the existence of the UKMSR had influenced what relevant, useful data could be collected from pwMS and have utility to researchers, but would that data be relevant to people with the disease and their clinicians, and could this data be supplemented with additional tests such as CoRe (discussed in Chapter 6 and referred to in this paper as MSiDMT at this early stage of development).

To that end we carried out a number of patient and public involvement events (PPI) with people with MS from Barts and the London NHS Healthcare Trust. At this I presented the

proposed 'feedback' page for the Register, where people with MS could opt-in (explicitly, off by default) to viewing their results on PRO completion, and then a composite page where all their responses could be viewed together with their medications, symptoms, and other relevant information. Some elements, such as webEDSS and MSIS, could be presented as a graph showing all completed values up to the most recent, with explanations of what the various instruments measured. This could then be printed and taken to clinical teams, or simply displayed to clinical staff. A version was also shown of a mock up of these instruments alongside dedicated tests that the Barts team would carry out (such as an ABILHAND upper limb measure, a Nine-Hole Peg Test, and others). They illustrated how these elements could be part of a clinical overview page to aid clinical decision making within a hospital setting.

Results

The fundamental insights from the PPI group on this data was an understanding that pwMS wanted the UKMSR portal to enable them to (i) have better control over their healthcare and treatment options, (ii) access clinical trials, and (iii) improve self-management. This encouraged us to enable the new feedback area of the MS Register to all members of the UKMSR, should they choose to see it.

Allowing people with MS to carry out self monitoring of their disease using the broad spectrum of PROs deployed in the UKMSR would allow pwMS to be more proactive in the management of their disease, and potentially allow for increased shared decision making with their healthcare professionals.

Paper 6: Can we improve the monitoring of people with multiple sclerosis using simple tools, data sharing, and patient engagement?

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Can We Improve the Monitoring of People With Multiple Sclerosis Using Simple Tools, Data Sharing, and Patient Engagement?

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Technological innovation is transforming traditional clinical practice, enabling people with multiple sclerosis (pwMS) to contribute health care outcome data remotely between clinic visits. In both relapsing and progressive forms of multiple sclerosis (MS), patients may experience variable disability accrual and symptoms throughout their disease course. The potential impact on the quality of life (QoL) in pwMS and their families and carers is profound. The introduction of treatment targets, such as NEDA (no evidence of disease activity) and NEPAD (no evidence of progression or active disease), that guide clinical decision-making, highlight the importance of utilizing sensitive instruments to measure and track disease activity and progression. However, the gold standard neurological disability tool—expanded disability severity scale (EDSS)—has universally recognized limitations. With strides made in our understanding of MS pathophysiology and DMT responsiveness, maintaining the status quo of measuring disability progression is no longer the recommended option. Outside the clinical trial setting, a comprehensive monitoring system has not been robustly established for pwMS. A 21st-century approach is required to integrate clinical, paraclinical, and patient-reported outcome (PRO) data from electronic health records, local databases, and patient registries. Patient and public involvement (PPI) is critical in the design and implementation of this workflow. To take full advantage of the potential of digital technology in the monitoring and care and QoL of pwMS will require iterative feedback between pwMS, health care professionals (HCPs), scientists, and digital experts.

Keywords: multiple sclerosis, monitoring, 3TEST, patient engagement, technology

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS). MS affects more than 130,000 people in the UK and over 2.5 million worldwide (1–3). While prediction of the disease trajectory in individual people with MS (pwMS) remains challenging, accrual of chronic disability is the norm (4, 5), particularly if pwMS are left without disease-modifying treatment (DMT) (6). Dependable outcome measures

are highly desirable to assess the clinical course of MS and inform patient management. Given the heterogeneity of clinical presentation, systems involved, and speed of progression, assessing outcomes in pwMS requires systematic, multidimensional tools. Comprehensive follow-up of pwMS has been demonstrated in a number of clinical trials (7–10). However, systematic monitoring of pwMS in clinical practice is often incompatible with the limited time available for patient review (11), particularly when using the expanded disability status scale (EDSS) (12), which nevertheless remains key to determine DMT eligibility (13), and despite its well-rehearsed shortcomings (14).

PwMS with advanced disease, for example those having an EDSS $\geq$ 6.5, and elderly pwMS are at particular risk of being less carefully followed up (15). These patients are more likely not on a licensed DMT and are commonly considered "beyond" immunotherapy, despite mounting evidence that neurologic function can potentially be preserved, even at a later stage of the disease (16, 17).

Here, we provide a perspective on using a new approach of collecting data in pwMS that combines (i) clinical assessments with potential for self-monitoring and (ii) patient-reported outcomes (PROs) using a platform shared between a large data repository, the UK MS Register at Swansea University, and BartsMS in east London, UK. We describe how such point-of-care data collection may serve both research and the individual pwMS in clinic and highlight the role of patient and public involvement (PPI) in facilitating the "buy-in" of pwMS underpinned by some preliminary data on patient engagement with the UK MS Register portal and corresponding data sharing preferences.

QUANTIFYING NEUROLOGIC DISABILITY

The introduction of the EDSS (12) as the key outcome measure of disability in MS DMT trials cemented its role as the neurologist's "gold standard" rating scale of disability in pwMS. However, while clinical trials usually allocate sufficient time to complete and fully document an EDSS (which takes ∼20–30 min), the time constraints of clinical practice regularly lead to either an "estimated" EDSS, or systematic clinical assessments remain patchy, or are not undertaken at all (11). To overcome this shortcoming, various versions of a patient-reported EDSS (PREDSS) have been proposed. These are either paper based, administered via telephone, or, more recently, via an online application, the "webEDSS" (18). Correlation has been observed between EDSS and all versions of PREDSS; however, limitations of agreement were identified, particularly at low EDSS levels (11). However, even if these limitations could be minimized, the non-parametric character of the EDSS, its ambulatory bias, and lack of sensitivity at high values remain problematic. Moreover, decline in cognitive function is not well covered, in spite of its key importance in pwMS, especially given the implications for employment opportunities (19, 20).

As a result, the National MS Society's Clinical Outcomes Assessment Task Force started more than 25 years ago developing a new set of outcome measures. Ultimately, a set of three tests was agreed, making up what was coined the Multiple Sclerosis Functional Composite (MSFC). The MSFC consists of the Paced Auditory Serial Addition Test (PASAT), Timed 25-foot walking (T25ftWT), and the Nine Hole Peg Test (9HPT) and has been implemented in a number of clinical trials (21). However, only this year, 2020, will a DMT licensing trial for the first time use one element of the MSFC, the 9HPT, as its primary outcome measure (22).

"BartsMS" is a clinic–academic partnership based at The Royal London Hospital (Barts Health NHS Trust) and The Blizard Institute/Queen Mary University of London providing clinical care to over 3000 pwMS. Faced with the same discrepancy between high expectations and the reality of limited resources (6), BartsMS introduced a modified version of the MSFC in their clinical practice in 2016. While T25ftWT and 9HPT were retained, PASAT was replaced with the Symbol Digit Modality Test (SDMT; oral version) following the recommendation by Drake and coworkers (23), among others (24). The SDMT has equal psychometric validity to the PASAT and is associated with lesser confounding by training and more congenial for both patient and assessor (23). It takes less time to complete, requires less expertise and experience of the assessor, and, unlike the PASAT, does not require special equipment for auditory presentation of stimuli (24). In practice, we summarize the three elements (T25ftWT, 9HPT, and SDMT) simply as "3TEST." Given a clinical and research focus of BartsMS on advanced MS, i.e., people with an EDSS of $\geq$ 6.5 (25), the ABILHAND questionnaire is also regularly administered to capture perceived manual ability (26). Obtaining such "real world" outcome measures in routine clinical practice and trials has also been recognized by the European Medicines Agency (EMA) as an important component of disease management (27).

THE EVOLVING ROLE OF REMOTE SELF-MONITORING

The relative simplicity of the MSFC or variations thereof, such as the 3TEST, combined with advances in technology and ever-increasing online resources and capabilities have led to the expansion and uptake of self-monitoring applications (28). Self-monitoring enables tracking the disease course in pwMS unable to travel to clinic, e.g., due to their disability or them living in remote locations. Given the often-extended intervals between follow-up in clinic (commonly 6–12 months), systematic self-monitoring may improve detection of changes not captured during visits, including relapses and disability accrual, thereby enabling earlier detection of disease progression and trajectories of long-term outcomes. Moreover, self-monitoring has inherent potential to empower pwMS to manage their condition pro-actively, with likely benefits for their care and self-management (29). Alongside other measures, such as written decision aids (30), self-monitoring may help remove hierarchical barriers and level the platform for shared decision-making between health care professionals (HCPs) and pwMS. It would be expected that such change will improve treatment satisfaction and adherence (31). Against this backdrop, numerous self-assessment tools

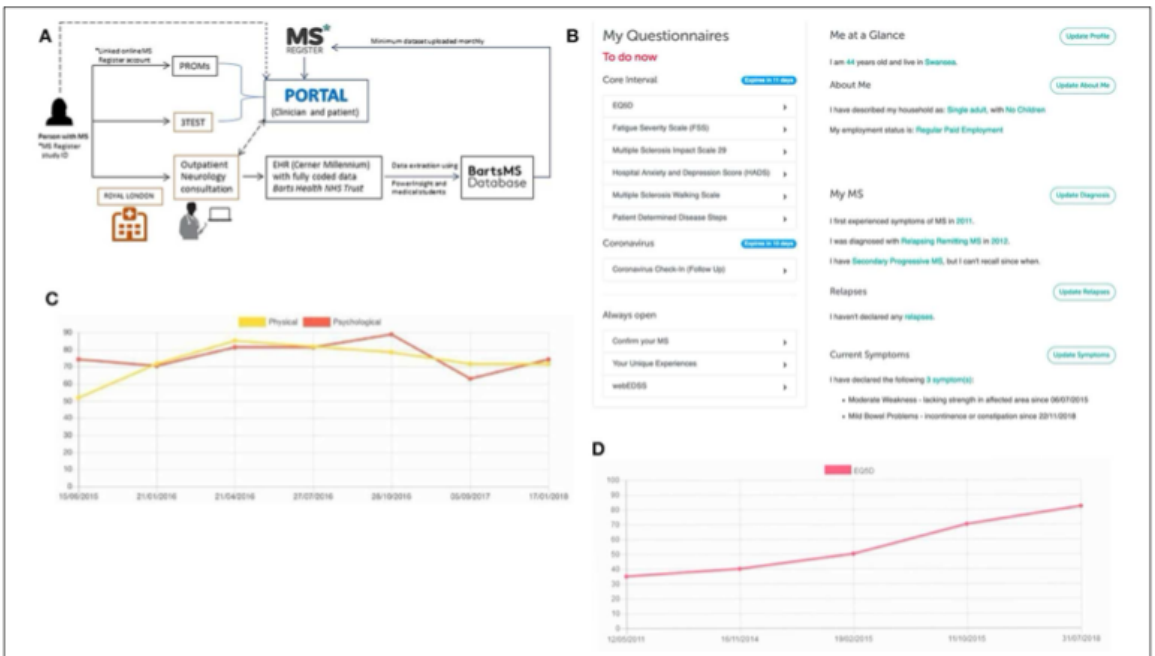

FIGURE 1 | The hub/spoke system between BartsMS and the UK MS Register. **(A)** The interaction between the BartsMS service & Database, and the UK MS Register. **(B)** My MS Hub page on the patient portal. **(C)** Graph of Multiple Sclerosis Impact Scale (MSIS29 V2) results viewed in the patient portal. Accompanying description for people with MS: "Used to measure the impact that your MS is having on you physically and psychologically at any given time. This questionnaire was designed specifically for MS. It means that researchers can measure how much your MS affects your quality of life. It is increasingly being used in MS research and clinical settings. What the graph means: the MSIS is composed of three scores, a total, a psychological sub-score and a physical sub-score. In this graph we show the psychological and physical sub-scores. In both Scales, higher values indicate that your MS is causing you more trouble and lower ones indicate less impact." **(D)** Graph of EQ-5D 3L results viewed in the patient portal. Accompanying description for people with MS: "This is one of the most commonly used health status measurements. It is not MS specific and so it can be used to make comparisons with various other health conditions/chronic diseases. What the graph means: the EQ5D has five questions specifically related to aspects of your general health and one scale marked out of 100 in which you indicate your overall quality of life. High scores indicate a better overall quality of life".

have been developed (32, 33). As part of this effort, our group developed portable versions of the 9HPTs and the T25ftWTs (34, 35), while the UKMSR produced an online version of the SDMT (MSiDMT) (36).

In addition, wearable technologies, including motion detecting devices (MTDs) and smartphone applications may facilitate minimally intrusive assessment of outcomes such as step count, walking speed, and gait (37) and support neurorehabilitation (38).

A MODEL OF INTEGRATED MONITORING AND PATIENT ENGAGEMENT

Results from tests that (i) are relatively straightforward to implement in clinic and (ii) can be translated into self-monitoring tools can be combined with PRO questionnaires and fed into the patient record, which, in health care settings covering large numbers of pwMS, is usually an electronic health record (EHR). EHRs facilitate the timely recording of patient data and the simultaneous navigation by multiple HCPs from different specialities (39). Coding terminology, such as Systematized Nomenclature for Medicine (SNOMED), provides a powerful resource to collate individual patient data as well as to identify, stratify, and audit patient cohorts and outcomes.

We use the generic Barts Health NHS Trust-wide EHR Cerner Millennium Clinical Record System (CRS). This system enables extraction of coded information to populate our database of pwMS (the "BartsMS Database") in Excel (40), thereby providing both an individual record and a point-of-care data collection, including 3TEST data, fed by the various HCPs at the Trust involved in the care of the pwMS. Our dataset is further enriched by the UK MS Register (UKMSR), an MS Society (UK)-sponsored resource that collects PRO data on pwMS throughout the UK (41). The UKMSR was conceived on the understanding that PRO data are important to capture the experience of pwMS and their families, friends, and carers (42–44). PROs are also commonly used as secondary endpoints in clinical trials to determine and compare the effect of DMTs. The core validated instruments collected by

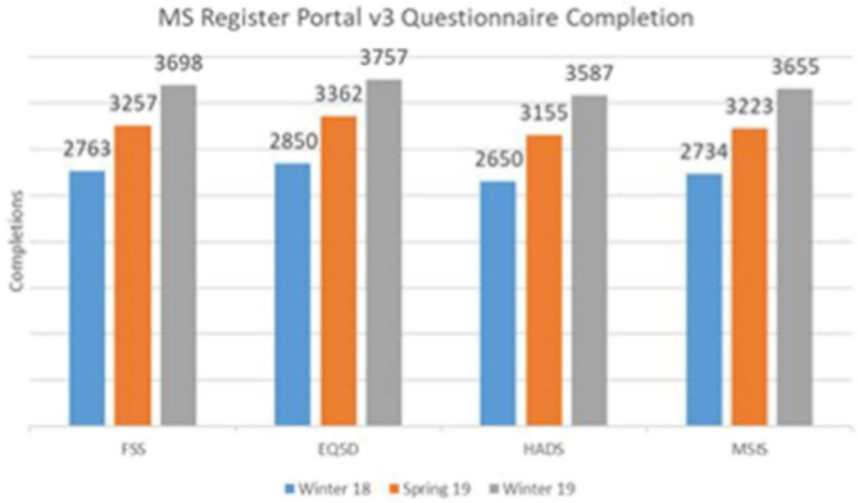

FIGURE 2 | Core Questionnaire Response rates following PPI and redesign of the UK MS Register portal.

the UKMSR are EuroQol 5D (EQ-5D), Multiple Sclerosis Impact Scale 29v2 (MSIS-29), Hospital Anxiety and Depression (HADS) Scale, Fatigue Severity Scale (FSS), the Multiple Sclerosis Walking Scale (MSWS-12), and Patient Determined Disease Steps (PDDS) (45–51). The webEDSS is also available as an *ad hoc* questionnaire (52).

Since 2017, BartsMS and the UKMSR have been developing a hub/spoke monitoring system (**Figure 1**). The intention of the algorithm is to (i) facilitate research through high-quality data collection, (ii) support the clinical service provision with PRO data, and (iii) enable the latter via a patient portal. PwMS who consent to join the UKMSR will have their minimum dataset (demographics, MS history, risk factors, disease course, EDSS scores, relapses, DMT, and symptomatic information) collected and securely uploaded via a REDCap electronic clinical record form (53). In addition, pwMS are prompted via email, at regular (currently 6-monthly) intervals, to fill in PRO questionnaires. This information can then be linked to their unique study ID provided at the hospital site, and thereby merged with their clinical record.

PATIENT ENGAGEMENT

We learned that patient and public involvement (PPI) is pivotal to maintain and expand data collection through the UKMSR. Valuable insights and feedback were provided through a PPI meeting held at The Royal London Hospital (Barts Health NHS Trust) on 16 February 2018. Key outcomes of this engagement day were (i) a re-designed, visually more attractive website enabling easier navigation and providing better sectioning, including a "My MS" hub page. This hub contains easily identifiable and accessible open questionnaires, including estimates of the time required for completion. This feature also provides pwMS with a snapshot of the information they have contributed and highlights any data that they should still provide; (ii) radio boxes for questionnaires, rather than drop-down menus since less mouse movement is required, making it easier to navigate for pwMS with upper limb function impairment; (iii) reduced frequency of questionnaire responses requested (bi-annually instead of quarterly); (iv) more tangible benefits for UKMSR subscribers, who were keen to receive comprehensive feedback about their collected questionnaire data—we therefore decided that the facility of viewing personal response data should be provided as an option; (v) since September 2018, participants who join the UKMSR and opt in to feedback are being offered a downloadable version of their results. By December 2019, 67% of new subscribers (total n = 2712) had had opted into this facility. This is designed so that it can be taken along to clinic appointments. Information is displayed in easily accessible graphs, allowing pwMS to track their condition over time. Explanations in lay terms are included about what the instruments and graphs mean and their relevance to pwMS (**Figures 1C,D**).

Further insights from our PPI exercise included an understanding that pwMS wanted the UKMSR portal to enable them (i) to have better control over their health care including treatment options, (ii) access to clinical trials, and (iii) improved self-management. PwMS were also passionate about furthering research both for short-term benefit and for future generations, including their own children.

To estimate the effect of our response to the PPI input received on the rate of questionnaires, we extracted the number of completed questionnaires at three time points; Winter 2018 (before implementation of the above changes to the portal),

Spring 2019, and Winter 2019. Data were extracted from the UKMSR production databases running Microsoft SQL Server 2014.

Figure 2 illustrates a significant increase in the number of completed questionnaires between the launch of the new website in Winter 2018 and the latest cutoff in Winter 2019. This increase suggests a significant impact of PPI on the new UKMSR portal design and functionality.

DISCUSSION

Optimizing the landscape of individualized, effective, and compassionate care with and for pwMS remains a work in progress. Whereas clinical trials provide data on a cohort level, the evidence produced can only provide a backdrop for decisions that need to be tailored to the individual pwMS. Clinical monitoring is essential to detect treatment success and failure, in order to make individual decisions. While various digital tools for disease monitoring in pwMS have been developed, their value in clinical practice is not yet established, and their adoption limited (54). We found validated measures that are easily applicable and straightforward to interpret a useful way to quantify change in an era where pwMS expect their care to catch up with the efficacy of the latest DMTs. The administration of 3TEST does not require any special qualification—virtually any HCP can be trained to apply it in a short timeframe. Since all three parts of the 3TEST can be done remotely, the limit for self-monitoring is now mainly a question of frequency and logistics (how often to test, how to feedback results to the health care team, and how to embed the data in the daily routine of neurologists and MS specialists between appointments). The simplicity and compatibility for remote testing of 3TEST also highlight the potential for relatively straightforward multi-center adoption and inclusion in large datasets, such as the UKMSR or MSBase (55), and there is obvious potential for remote testing in exceptional situations, such as a pandemic (56). Furthermore, 3TEST is likely going to be of use when screening for trials where measures other than the EDSS are being used for inclusion as well as outcome (22). New systems intended to both serve individual monitoring of pwMS and contribute to large datasets, such as Floodlight (33, 57), will need to be validated using well-established tests such as those combined in 3TEST (32).

Our experience trying to combine clinical and PRO data collection via the UKMSR in order to facilitate databasing for research, service audit, and individual patient care highlights the important role of PPI throughout the design and implementation process. To truly deliver patient-centered care and at the same time enable high-quality data collection, any system for pwMS needs to be developed jointly with pwMS. In our example, PPI led to a significantly increased number of completed PRO questionnaires. We are currently optimizing and streamlining mutual data exchange between BartsMS and the UKMSR to provide an integrate model of point-of- care data collection. This system may provide a model of data collection and sharing that can be adopted by other centers across the UK and beyond.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

KS initiated the BartsMS Database and conceptualized the setup between the UK MS Register and BartsMS clinical interface, which the team helped establish. KA-P, RM, and KS drafted the manuscript. CA, AS, and KT-D contributed toward the subsequent revisions. RM and EB performed the data extraction and analysis. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors KS.

Conclusions

The result of the work to show direct feedback to people with MS to a large and interested patient group was extremely informative and expanded the initial work done in the development of the Register. In this paper, we examined the impact of involving people with MS in the creation of feedback mechanisms to provide some measure of condition monitoring for themselves and their clinicians. This demonstrated the depth of involvement that pwMS have with their condition and their desire to see and understand this data; it also cemented the need to continually improve the personalised feedback available to participants on the UK MS Register.

This reinforced the value of directly involving people with MS in the design of the UKMSR. This ability for people to be better informed of their own condition remains unique to the UKMSR to this day. Participants can chart the consequences of the disease across a number of domains, and also to share this information with their clinicians should they choose to. This is something that has become more expected in the general population; it is becoming the norm to count steps, fitness minutes or calories on wearables and smart phones. This expectation to become more involved with the maintenance and understanding for your own health and disease is important. Patients that have become 'activated' or health-aware are more likely to have better health-related outcomes than those that are more passive in the management of their condition (Greene and Hibbard, 2012), (Grogan Moore et al., 2019). Though there is an argument that the act of participating in research (and a disease register specifically) illustrates a degree of activation that would not be present otherwise, enhancing this involvement with self-management can only be beneficial for the patient and their clinicians.

An important aspect of the UKMSRs work that needs to be better represented are the efforts made to ensure that the clinical and portal populations recruited to the Register are representative of the UK MS population. Whilst the gender ratio is correct (3:1 female to male), the balance of people from other ethnicities is certainly not. The UKMSR, as with multiple other UK and worldwide research populations, consists of an overwhelmingly homogenous population of white European participants (Onuorah et al., 2022). This trend is even present in most recent COVID work (Murali et al., 2023) and the belief that MS was a disease primarily of white populations persists even in MS research from less than 6 years ago (Albor et al., 2017) despite people from other ethnic backgrounds potentially having worse long-term outcomes (Alsaeed et al., 2018). There are multiple factors at work here however: there may be cultural issues with people from other ethnicities taking part in research due to difficulty admitting ill-health to family or friends, it could be economic (if they are unable to take time off work to attend a health care professional), or it could be educational. Participants need to know the system, or at least be able to learn about it, in order to make use of it; and more highly-educated people may have jobs where it is easier to take time off work. Much of this needs to be unpacked as research generally uses indices of multiple deprivation (of which education is one factor) as a proxy. Some work we have done as a Register points to an association between deprivation and access to disease modifying therapies (Das et al., 2022). This is currently being developed with a paper submitted to the Multiple Sclerosis Journal analysing the impacts of education.

As a more definitive step, we also made the collection of ethnicity data mandatory from

clinical sites and on the portal.

Publishing and highlighting ethnicity data in the clinical and portal elements of the Register is an area that we are now more proactive about. We regularly attend and speak at patient events such as Asian MS and The Nerve of my MS and are working with the ADAMS initiative (Jacobs et al., 2023) as a means of recruiting people from broader ethnicities into research. Of course, diversity is a broader topic than just ethnicity, although the Register does not collect information related to religion, we actively engage with members of the LGBTQ+ community to ensure that we can be as representative as possible in the language that we use.

This work that went into this paper provides people with MS with a way to become more 'activated', and potentially provide their clinicians with more information about them. It illustrated a unique element of the UK MS Register, enabling even better engagement and more reason for people to come back and answer the questionnaires every six months. There was a discernible value; you could see your disease changing over time. Beyond the altruistic desire of Register participants to contribute their time and data for MS research, this could prove a powerful motivator.

Following the input from people with MS and with all the changes in place, the number of users returning to the MS Register has shown almost continual improvement since 2018. Figure 5 below shows the completed 'core' questionnaires on the UK MS Register before and since the changes to the feedback were implemented. This is a continuation of the image shown in the paper above, where just the initial two years of responses were shown. Correlation is not proof of causation and there are a number of potential factors here. However, the sustained increase in visitors shows that there was a positive response to the changes on the portal.

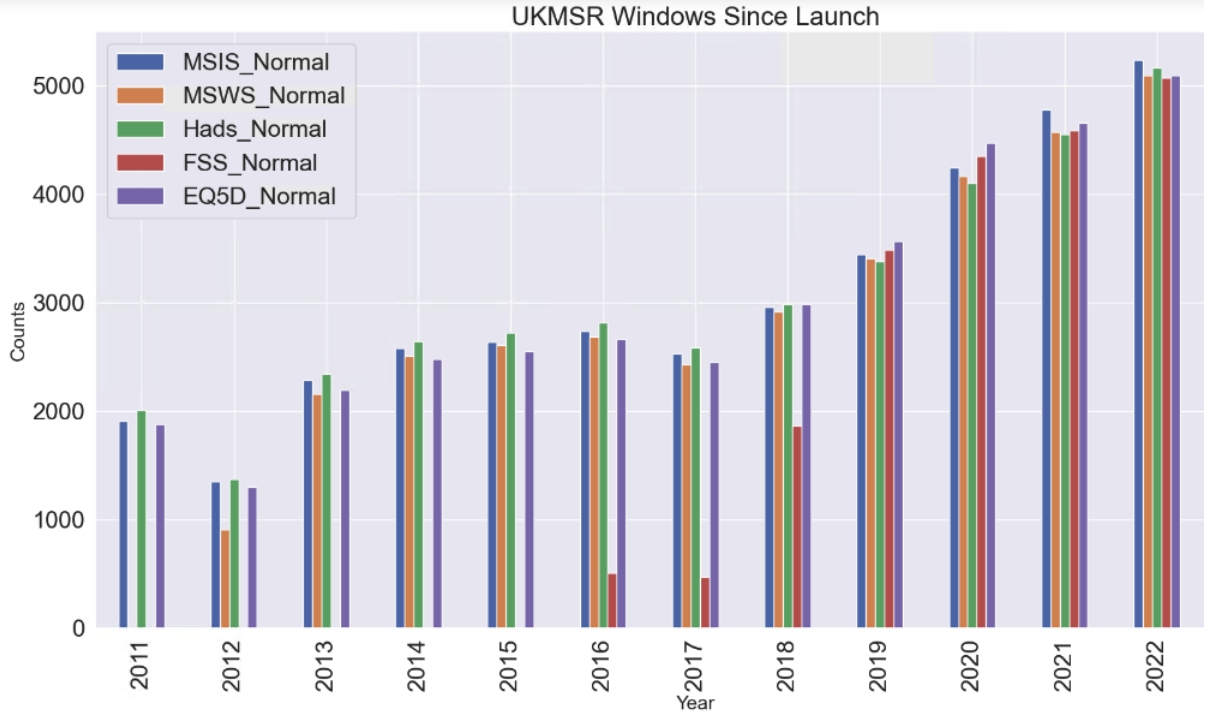

Figure 5 : UKMS Register questionnaire completions following PPI modifications

MSIS : Multiple Sclerosis Impact Scale, MSWS : Multiple Sclerosis Walking Scale, HADS : Hospital Anxiety and Depression Scal, FSS : Fatigue Severity Scale, EQ5D : EuroQOL 5 Dimensions of Life

The timing of this research and change to the Register could not have come too soon; in 2020 the MS Register would be called upon to become even more of a vital cog in the MS research within the United Kingdom. The ability of people with MS to have a reference to the state of their disease when unable to see a clinician, and for the UKMSR to be able to remotely capture novel data from the very outset of a global pandemic, would prove to be critical.

Chapter 8: COVID-19 is associated with new symptoms of multiple sclerosis that are prevented by disease modifying therapies

Background

The UK MS Register had been engineered to a point where it was a trustworthy repository that people with MS would contribute to, and a resource for them to monitor the impact of their disease. It had also developed a flourishing complement of researchers who were using it for their own work, distributing bespoke questionnaires complementing and linking to the PROs routinely gathered in six-monthly windows ((Baker et al., 2016), (Campbell et al., 2017), (Goodwin et al., 2018)).

The worldwide SARS-CoV-19 (COVID-19) pandemic that started in early 2020 represented a significant health threat across the globe resulting in more than 6 million deaths ("WHO Coronavirus (COVID-19) Dashboard," n.d.). For people with MS, who were potentially immunocompromised through pre-existing infection (Marrodan et al., 2019) or treatment, new data was vital. The MS Register was in an ideal position to contribute valuable data to a number of COVID-19 initiatives and provide research data to people with MS and their clinicians.

In collaboration with senior clinicians, people with MS and representatives from patient organisations we formed a group determined to collect data vital to data discovery for MS research during the pandemic. We designed a sequence of questionnaires that would capture data about SARS-COV-19 from people with MS (Evangelou et al., 2020), their clinical teams, their mental health, (Garjani et al., 2021) their opinions to COVID-19 and in one case, from an independent healthy population to act as a control cohort.

This work, specifically examining those people with MS who had symptoms consistent with positive COVID-19 cases were asked to complete a bespoke questionnaire regarding the exacerbation of existing MS symptoms, or development of new ones.

My input

I was responsible for management of the internal and external meetings required to achieve consensus of questionnaire design and implementation, analysis, data provision, editing and proofreading. More fundamentally, this work formed part of a sequence of activities around COVID-19 (as can be seen in the references). This paper and data from the UKMSR were submitted to another international initiative (Simpson-Yap et al., 2021) describing the impacts of DMT and COVID-19 in MS.

For this specific issue we designed and deployed an enhanced questionnaire to elicit all known symptoms of COVID-19 at that time – a factor that changed as the pandemic progressed and different variants emerged. Methods of confirming diagnosis of COVID-19 also changed as the availability of effective laboratory COVID-19 testing and accurate lateral flow tests were rolled out across the UK. These developments had to be sequenced within

the existing 'suite' of COVID-19 questionnaires that had been added to the MS Register.

Methods

We invited 978 people with confirmed COVID-19 diagnosis to complete our additional MS symptoms questionnaire with 404 (41%) responding. These pwMS had already completed the initial COVID-19 monitoring questionnaire that we had added and were reminding people of every 6 weeks. 57% of these responders declared exacerbations of their MS symptoms, the majority of these being worsening of pre-existing symptoms. Given the complexities of the analysis (due to the sheer number of potential confounding variables) we carried out directed acyclic graphing to mediate these. The results of this analysis can be seen in Table 3 from Paper 7 (below).

Table 3 : Factors associated with changes in symptoms of multiple sclerosis

Factors associated with changes in symptoms of multiple sclerosis.

	Multivariable regression analysis				Univariable regression analysis		
	OR	95% CI	N [a]	Adjustments	OR	95% CI	N [a]
Developing new MS symptoms (n = 82) compared to no new MS symptoms (n = 322)							
Age (one-year increase)	No adjustment was required.				0.997	0.975–1.019	404
Male (vs female)	No adjustment was required.				0.550	0.289–1.048	403
PMS (vs RRMS)	1.532	0.814–2.883	395	Age, Sex, MS disease duration	1.337	0.779–2.296	404
MS disease duration (one-year increase)	1.024	0.991–1.059	395	Age	1.017	0.989–1.046	395
Pre-COVID-19 webEDSS score (one-point increase)	1.108	0.929–1.322	248	Age, Sex, Type of MS, Taking DMTs	1.059	0.914–1.226	248
Taking DMTs	**0.556**	**0.316–0.978**	404	Type of MS	0.563	0.341–0.928	404
Worsening of pre-existing MS symptoms (n = 207) compared to no worsening (n = 128) [b]							
Age (one-year increase)	No adjustment was required.				1.016	0.995–1.037	335
Male (vs female)	No adjustment was required.				0.640	0.381–1.077	335
PMS (vs RRMS)	1.147	0.625–2.106	327	Age, Sex, MS disease duration	1.328	0.786–2.243	335
MS disease duration (one-year increase)	**1.042**	**1.009–1.076**	327	Age	1.044	1.015–1.074	327
Pre-COVID-19 webEDSS score (one-point increase)	**1.251**	**1.060–1.478**	208	Age, Sex, Type of MS, Taking DMT	1.163	1.017–1.330	208
Taking DMTs	1.186	0.716–1.966	335	Type of MS	1.047	0.673–1.627	335

CI = Confidence Interval; DMTs = Disease Modifying Therapies; MS = Multiple Sclerosis; OR = Odds Ratio; PMS = Progressive MS, which includes primary and secondary progressive MS; webEDSS = web-based Expanded Disability Status Scale.

[a] Number of participants included in the analysis after listwise deletion of missing data.

[b] Sixty-nine participants did not recall whether their pre-existing MS symptoms had become worse or not during their COVID-19 infection.

Results

This analysis found that taking DMTs was associated with a reduction in MS symptoms; this would be the expected outcome of most DMTs but was particularly important to note in the presence of a COVID-19 infection. A limitation of the study was the inability to examine specific DMTs due to the relatively low numbers of responders per DMT. The conclusion that DMTs were safe could only really be made in the general case, but still provided evidence of overall safety. Our findings that COVID-19 overall caused a higher level of exacerbation than other previously reported systemic infections could be a factor of over-reporting by pwMS, rather than data directly gathered by clinicians but so far seems to be borne out by other international studies.

https://doi.org/10.1016/j.msard.2021.102939

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Supplementary Materials for this paper

Statistical analysis

Directed acyclic graphs (DAG) of the COVID-19 and MS Symptoms study were created using DAGitty, a browser-based environment for creating, editing, and analysing (Directed Acyclic Graphs) DAGs (http://www.dagitty.net/). The DAG model is provided in Figure 6.

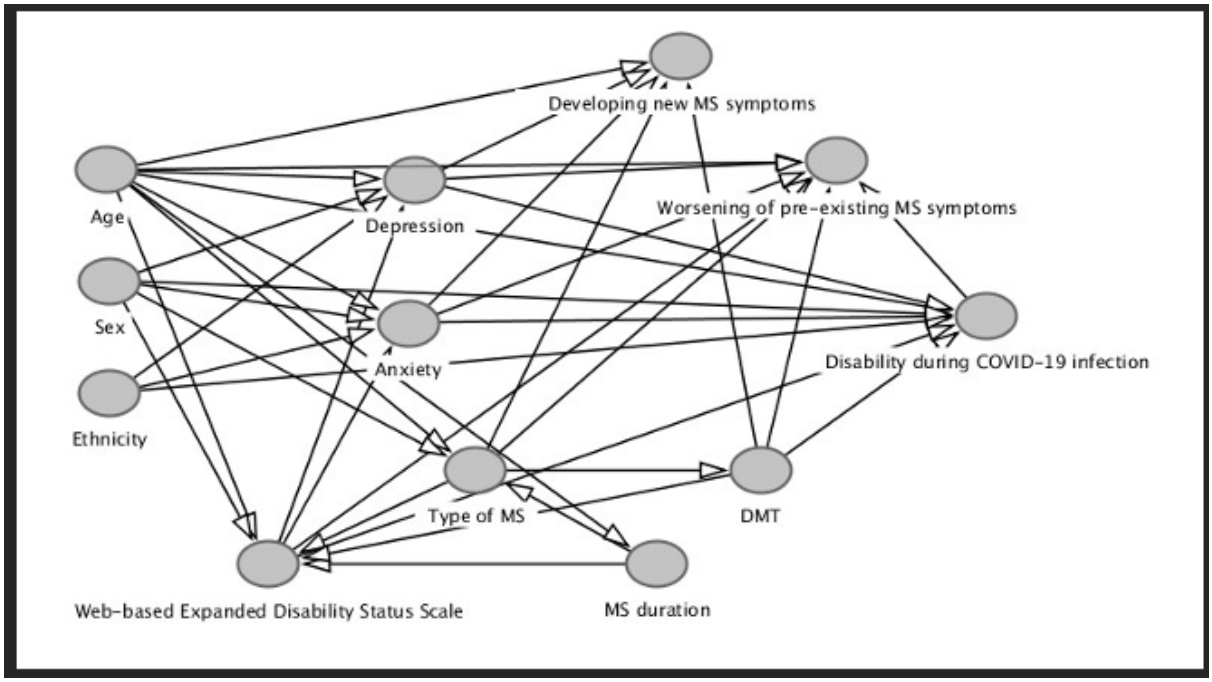

Figure 6 : Directed acyclic graphs (DAG) of the COVID-19 and MS Symptoms study

The following DAG code can be used to reproduce the model using DAGitty:

```
dag {

bb="0,0,1,1"

"Developing new MS symptoms" [pos="0.551,0.324"]

"Disability during COVID-19 infection" [pos="0.735,0.562"]

"MS duration" [pos="0.536,0.790"]

"Type of MS" [pos="0.427,0.704"]

"Web-based Expanded Disability Status Scale" [pos="0.302,0.791"]

"Worsening of pre-existing MS symptoms" [pos="0.645,0.420"]

Age [pos="0.204,0.428"]

Anxiety [pos="0.386,0.569"]

DMT [pos="0.599,0.704"]

Depression [pos="0.390,0.437"]

Ethnicity [pos="0.206,0.633"]

Sex [pos="0.206,0.530"]

"Disability during COVID-19 infection" -> "Worsening of pre-existing MS symptoms"

"MS duration" -> "Type of MS"

"MS duration" -> "Web-based Expanded Disability Status Scale"

"Type of MS" -> "Developing new MS symptoms"

"Type of MS" -> "Web-based Expanded Disability Status Scale"

"Type of MS" -> "Worsening of pre-existing MS symptoms"
```

"Type of MS" -> DMT

"Web-based Expanded Disability Status Scale" -> "Disability during COVID-19 infection"

"Web-based Expanded Disability Status Scale" -> "Worsening of pre-existing MS symptoms"

"Web-based Expanded Disability Status Scale" -> Anxiety

"Web-based Expanded Disability Status Scale" -> Depression

Age -> "Developing new MS symptoms"

Age -> "Disability during COVID-19 infection"

Age -> "MS duration"

Age -> "Type of MS"

Age -> "Web-based Expanded Disability Status Scale"

Age -> "Worsening of pre-existing MS symptoms"

Age -> Anxiety

Age -> Depression

Anxiety -> "Developing new MS symptoms"

Anxiety -> "Disability during COVID-19 infection"

Anxiety -> "Worsening of pre-existing MS symptoms"

DMT -> "Developing new MS symptoms"

DMT -> "Disability during COVID-19 infection"

DMT -> "Web-based Expanded Disability Status Scale"

DMT -> "Worsening of pre-existing MS symptoms"

Depression -> "Developing new MS symptoms"

Depression -> "Disability during COVID-19 infection"

Depression -> "Worsening of pre-existing MS symptoms"

Ethnicity -> "Disability during COVID-19 infection"

Ethnicity -> Anxiety

Ethnicity -> Depression

Sex -> "Disability during COVID-19 infection"

Sex -> "Type of MS"

Sex -> "Web-based Expanded Disability Status Scale"

Sex -> Anxiety

Sex -> Depression

}

Conclusions

At that point in time, the greatest fear for many people with MS and their treating clinicians was that the DMTs that were being prescribed may become actively dangerous in the presence of a COVID-19 infection. In this paper we looked at the effect the underlying COVID-19 infection had on multiple sclerosis symptoms.

This single paper illustrated the power of the UKMSR as a platform. It utilised a specific instrument, delivered at scale to a research-active population. It enabled us to carry out an effective analysis based on the volume of linkable related datasets that were accessible from the participants in the Register study. With the notable exception of the national 'Zoe' study (Menni et al., 2020) there were very few other instances of longitudinal research at scale that combined data in this way.

This paper also demonstrated that a lot of the earlier arguments about the 'validity' of the population had been conquered. Paper 4 (in Chapter 5), combined with more acceptance over time of PROs and the presence of a global pandemic, seemed to turn it into a non-issue. When the papers generated during the pandemic were submitted to journals, none of the peer-reviewers questioned the veracity of the population.

The COVID-19 pandemic itself demonstrated the utility of the Register, not only in the production of essential research data, but also as a means of engaging with people with MS by involving them more closely in research, and by informing them of the impact that their data donation was having. I produced multiple videos over the course of the pandemic, releasing them on YouTube (“UK MS Register - YouTube,” n.d.) with appropriate links and information via social media channels such as Twitter (“UKMSRegister (@UKMSRegister) / Twitter,” 2023). These gave updates about the status of the research, how many participants had been recruited to the various instruments, and if there were updates to any guidelines or publications.

From an informatics point of view this paper demonstrated all of the components of the UKMSR working efficiently together; from the point of project approval, questionnaire design and prototyping; through deployment and data gathering; to linkage and deployment of anonymised data to the secure eResearch Platform so that the team from Nottingham could have secure up-to-date access to this data. This showed that results could be produced urgently and at scale, in a governed and secure way.

The next paper in this thesis also comes from the COVID-19 pandemic; this time using data coming directly from clinical sites. While clinical sites have always been a vital element of the Register, Paper 8 shows an ability to engage deeply with clinicians, even when their site is not expressly a part of the Register.

Chapter 9: COVID-19 in multiple sclerosis: clinically reported outcomes from the UK Multiple Sclerosis Register

Background

The depth of COVID-19 data that the UKMSR had collected from people with MS was significant – over 100,000 completed questionnaires covering topics such as symptomatology, duration of infection, lateral flow results and potential post-traumatic stress disorder in the wake of the pandemic – all linked to each individual's responses to the Register's standard 'core' questionnaires.

To this PRO data I sought to add experiences from MS clinical treatment sites. This served to help gauge the impact on clinical services and to gather data on severe infection; the most ill would not be able to self-report on the online portal and without a specific instrument, MS treatment centres would have no way to report this information either.

Therefore with reference to the clinical group that had created the PRO elements for data capture, we designed an instrument suitable for data collection inside the NHS.

My input

For this paper I developed the initial questionnaire to be deployed, implemented the design with the prototype environment in the UKMSR platform, sent emails inviting sites to respond, carried out follow-up and information to those sites to ensure that recruitment was present in the minds of busy NHS staff. I carried out analytical tasks with the second author on the paper, wrote the initial draft, proofread and incorporated suggestions from other authors, submitted the paper to the journal, and responded to reviewer comments.

Methods

Following on from the pwMS supplied COVID-19 data, we had also designed a data collection form so that *any* clinical site in the UK could supply anonymised COVID-19 infection data about MS patients, with particular emphasis on patient recovery or death. The data collection period at the time of publication of the paper allowed us to examine the first two 'waves' of the pandemic and the changes that occurred in clinical responses and behaviour within them.

All MS specialist treatment centres in the UK were encouraged to supply data to the UKMSR eCRF (electronic Case Return Form) via social media and an email invitation with the appropriate link. Minimal relevant demographics were sought; age, gender and region. Next COVID-19 specific data were required, (including how the COVID-19 infection was confirmed), then MS-specific data including age at diagnosis, MS type, DMT status and EDSS score. We additionally asked for information relating to comorbidities, specifically relating to cardiovascular, respiratory, and 'other'. Lastly, outcomes were categorised as 'not hospitalised', 'hospitalised, alive' and 'hospitalised, deceased'.

We carried out multiple statistical tests on the data including ANOVA (Kruskal-Wallis in small n) and Chi-Square (Fisher's Exact in small n). The evolving nature of COVID-19 and treatment methods from the outset of the pandemic necessitated a number of analyses and statistical approaches.

Results

We collected data on 292 patients with MS from England, Wales, and Northern Ireland from 46 separate NHS hospitals. 68.5% were female and 59.3% had RRMS, median age was 50. 224 of the patients had EDSS scores prior to their COVID-19 infection; 78 (34.8%) were 'Mildly' disabled, 51 (22.8%) 'Moderately', and 95 (42.4%) 'Severely' disabled. 168 had a positive polymerase chain reaction (PCR) test.

In our analysis we found older age and male gender to be the most significant indicators for a poor outcome in pwMS – as was the case in the general population. Being on a DMT and not having progressive MS were predictors of a better outcome. We took our ordinal logistic regression model developed during the first wave on age and gender as predictors of survival and applied it to the second wave. The model had predicted outcomes in the first wave with an accuracy of 70.273% (CI 58.52%, 80.34%) Applying this model to the second wave found it to be 57.14% accurate (CI 46.75%, 67.10%), and 39/42 of the inaccurate predictions were for worse outcomes. Thus, the model that fitted the first wave predicted many more worse outcomes than occurred in the second wave. This showed that those hospitalised in the second wave were younger with better outcomes on the whole. Table 4 shows the population demographics between the first and the second waves of the pandemic.

Table 4 : Population demographics and clinical features of the first and second waves

Population demographics and clinical features of the first ($n = 74$) and second waves ($n = 98$). Tests were conducted using Chi Squared and analysis of variance (ANOVA). Kruskal-Wallis test was substituted for ANOVA where results were non-normal, and Fisher's Exact test was substituted for Chi Squared where expected values were small.

Characteristic	First wave $n = 74$	Second Wave $n = 98$	Standard Hypothesis test: p-value
Gender: Female/Male, missing	48/26, 0	72/26, 0	0.294
Age (Years): Median (IQR), missing	54 (44, 64), 0	46 (37, 54), 0	0.005
MS Type: progressive/not progressive, missing	36/33, 5	28/70, 0	0.003
EDSS Group: mild/ moderate/severe, missing	18/10/35, 11	38/24/29, 7	0.013
DMT: yes/no, missing	35/35, 4	67/31, 0	0.025
Hospitalised: yes/no, missing	51/23, 0	22/76, 0	<0.001
Deceased: yes/no, missing	8/66, 0	2/96, 0	0.020

Paper 8: COVID-19 in multiple sclerosis: clinically reported outcomes from the UK Multiple Sclerosis Register

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Original article

COVID-19 in Multiple Sclerosis: Clinically reported outcomes from the UK Multiple Sclerosis Register

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ABSTRACT

Background: In March 2020, the United Kingdom Multiple Sclerosis Register (UKMSR) established an electronic case return form, designed collaboratively by MS neurologists, to record data about COVID-19 infections in people with MS (pwMS).
Objectives: Examine how hospital admission and mortality are affected by disability, age and disease modifying treatments (DMTs) in people with Multiple Sclerosis with COVID-19.
Methods: Anonymised data were submitted by clinical teams. Regression models were tested for predictors of hospitalisation and mortality outcomes. Separate analyzes compared the first and second 'waves' of the pandemic.
Results: Univariable analysis found hospitalisation and mortality were associated with increasing age, male gender, comorbidities, severe disability, and progressive MS; severe disability showed the highest magnitude of association. Being on a DMT was associated with a small, lower risk. Multivariable analysis found only age and male gender were significant. Post hoc analysis demonstrated that factors were significant for hospitalisation but not mortality. In the second wave, hospitalisation and mortality were lower. Separate models of the first and second wave using age and gender found they had a more important role in the second wave.
Conclusions: Features associated with poor outcome in COVID-19 are similar to other populations and being on a DMT was not found to be associated with adverse outcomes, consistent with smaller studies. Once in hospital, no factors were predictive of mortality. Reassuringly, mortality appears lower in the second wave.

1. Background

Following the global pandemic of the novel SARS-CoV2 (WHO. Statement on the Second Meeting of the International Health Regulations 2005) infection (COVID-19), the UK population was required to 'lock-down', in the first instance from the 23rd March 2020 and eased on 14th August 2020 and again from the 5th November 2020 until the 2nd December 2020 in England (IfG, 2021a). People with MS (pwMS), some of whom experience chronic disability and/or receive immune-suppressing disease modifying drugs, have ongoing concerns and uncertainty around their risk of COVID-19. Given these uncertainties, there is an ongoing need to explore the impact of COVID-19 on people with MS. The UK Multiple Sclerosis Register (UKMSR) has been capturing longitudinal clinical and patient reported outcomes in

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since 2011 (Middleton et al., 2018). In March 2020, a platform was established to allow clinicians to record data about pwMS, both admitted to hospital and treated at home, due to COVID-19. The UKMSR provided an electronic case return form (eCRF), designed collaboratively by the UK MS research community and with reference to a similar initiative in Italy (Sormani, 2020), capturing data about the COVID-19 features, and the MS history. This form was made available, securely over the internet, to all MS neurologists in the UK. Given the rapid evolution of the symptomatology of the virus, it was important to capture a broad spectrum of measures, both about the COVID-19 infection and essential data specific to MS. There are a number of published clinical studies from the United States (Salter et al., 2021), Iran (Sahraian et al., 2020), Italy (Sormani, 2020), the Netherlands (Loonstra et al., 2020) and Scotland (Fernandes et al., 2020), but given differences in the impact of COVID-19, and the management of MS, throughout the world, it is helpful to understand how the infection impacts pwMS in different countries where different health systems operate and more specifically within the UK and how this has evolved over the pandemic.

2. Objectives

To report on hospitalisation and death in people with MS infected with COVID-19 in the UK, as recorded by MS specialist neurology centres through two peaks of disease in March 2020 and February 2021.

3. Methods

The UK MS Register has ethical approval from South-West Central Bristol Research Ethics Committee (16/SW/0194). All study data was anonymous. An eCRF was distributed to UK neurologists via email, social networks, and the UK Multiple Sclerosis Society.

The requirement for data entry was a confirmed diagnosis of MS by a UK Neurologist and that the patient must be resident in the UK. For the purposes of analysis, we excluded those without a confirmed COVID-19 infection, or with missing values for hospital admission status and outcome. The eCRF provided three options for confirmation of COVID-19 infection: a positive PCR test, positive SARS-CoV2 antibody test, or clinical confirmation based on presenting symptoms and other investigations e.g. typical chest imaging findings (Islam et al., 2021).

The eCRF was created using REDCap (Harris et al., 2009) and data were analyzed using the R language (R Core Team, 2018). Validation was integrated into the eCRF (Appendix 1), with few response options being made mandatory, to allow for the difficulties of clinical data capture during the ongoing pandemic and not limit data capture. For the purposes of pre-analysis, some sub-categories of data were aggregated, in accordance with clinical advice. MS types were combined into either 'progressive' (primary progressive MS and secondary progressive MS) or 'not progressive' (relapsing remitting MS). The Expanded Disability Status Scale (EDSS) scores were categorised as 'Mild' (EDSS 0–2.5), 'Moderate' (EDSS 3–5.5), and 'Severe' (EDSS $\geq$ 6). Details on the following comorbidities were collected: cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, other chronic lung disease, hypertension, cancer, stroke, chronic renal diseases, and chronic liver diseases. For analysis, these were aggregated into three categories of 'Cardiovascular' (cardiovascular diseases, hypertension and stroke), 'Respiratory' (asthma, chronic obstructive pulmonary disease and other chronic lung disease), and 'Other' (diabetes, cancer, chronic renal disease or chronic liver disease). Comorbidities were further aggregated into one yes/no measure of having 'Any Comorbidity' for some analyzes. A complete data dictionary is available on request.

Hospital admission (yes/no) and final recorded outcome (deceased/alive) were combined into a status variable of "not admitted to hospital, now alive/recovering" to "admitted to hospital, now alive/recovering" to "admitted to hospital, now deceased" to summarise serious events. This was treated as a sliding scale of serious events (1 - "not hospitalised, alive" - 2 ("hospitalised, alive") - 3 ("hospitalised, deceased") to perform univariable and multivariable ordinal logistic regression for demographic and clinical factors. The assumption of proportionality of odds was confirmed and Variance Inflation Factor (VIF) was calculated by converting the logistic model to a linear one, and t-tests, analysis of variance (ANOVA) and Pearson's correlation were used to further explore interactions between independent variables. Variables were excluded from the multivariable model in a step-wise backwards fashion.

Treating the three levels ("not hospitalised, alive", "hospitalised, alive", "hospitalised, deceased") as nominal categories instead, further standardised hypothesis testing was conducted with the null hypothesis being that there was no association between the variable and the three potential outcomes. Chi-Squared and ANOVA were used in the first instance, with Fisher's Exact substituted for Chi-Squared where expected values were small, and Kruskal-Wallis substituted for ANOVA where results were non-normal. Post-hoc pairwise comparisons using Bonferroni adjustment were calculated for factors achieving statistical significance (Table 2).

The demographic and clinical factors chosen for inclusion were sex, age, MS type, EDSS, DMT treatment, comorbidities, and lymphocyte count prior to COVID-19 infection. With regards to DMT treatment, serious events were primarily assessed in terms of whether or not a patient was receiving a DMT at the time of infection.

Some event-specific variables were examined separately for serious events of hospitalisation and death. For hospital admission, these included reasons for admission to hospital, duration of hospital stay, and signs and symptoms of infection. For mortality, signs and symptoms of infection, as well as severity, and respiratory support, were assessed.

Certain features of the approach to COVID-19 diagnosis and treatment changed over the course of the pandemic (of particular relevance here, given our inclusion/exclusion criteria, is that PCR tests became more readily available over time). To better understand the effects of these changes on our data, standard hypothesis tests (with a null hypothesis assuming no association) were used to compare population demographics and clinical features from the 'first wave' (defined here as 3rd March 2020 – 20th August 2020) and 'second wave' (21st August 2020–16th March 2021 – as the end of this study). An ordinal logistic regression, using the independent variables chosen previously, was modeled on the first wave data and used to predict outcomes in the second wave data, and vice versa. The models were then used to compare the predictions of each model to both sets of data.

4. Results

4.1. Demographics

Data on 292 individual pwMS (England: 232, Wales: 41, Northern Ireland: 15, unspecified location: 4) were entered by clinicians between 27th March 2020 and 16th March 2021. Median age was 50 with an interquartile range (IQR: 42, 60), 68.5% were female. One hundred and seventy-three (59.3%) had relapsing-remitting MS, 103 (35.3%) had progressive (primary or secondary) and 16 (5.5%) had unknown MS type. Two hundred and twenty-four had last known EDSS scores prior to COVID-19 infection; 78 (34.8%) were 'Mildly', 51 (22.8%) 'Moderately', and 95 (42.4%) 'Severely' disabled.

One hundred and sixty-eight (57.5%) pwMS had a positive polymerase chain reaction (PCR) test, 5 (1.7%) had a positive antibody test and 23 (7.9%) were clinically confirmed based on presenting symptoms and other investigations. Ninety-six (32.9%) pwMS were excluded because they did not have confirmed COVID-19 according to the methods specified. A further 3 patients were excluded because they had missing values for either hospital admission status or outcome. Demographics and clinical features for the 193 included pwMS are provided in Table 1.

Table 1
Clinical features of people with MS with confirmed COVID-19, with known hospital admission and outcome status. One person with MS who died at home was included in the 'Deceased, Hospitalised' category.

Characteristic (*denotes reference category for analysis)	Confirmed by Test (n = 193) Deceased, Hospitalised n = 16	Alive, Hospitalised n = 70	Alive, Not Hospitalised n = 107	*Univariable Analysis: Odds Ratio [95% CI], p-value*
Gender: Female*/ Male, missing	9/7, 0	39/31, 0	86/21, 0	2.93 [1.61, 5.37], <0.001
Age (Years): Median (IQR), missing	66 (58, 73), 0	58 (50, 72), 0	44 (36, 52), 0	1.10 [1.07, 1.13], <0.001
MS Type: progressive/not progressive*, missing	12/1, 3	45/21, 4	17/90, 0	14.17 [7.17, 29.38], <0.001
EDSS Group: mild*/ moderate/ severe, missing	0/1/13, 2	9/7/41, 13	51/30/20, 6	1.55 [0.53, 4.47], 0.416 15.94 [6.97, 39.97], <0.001
DMT: yes/no*, missing	2/13, 1	24/43, 3	81/24, 2	0.13 [0.07, 0.25], <0.001
Comorbidities:				
Cardiac: yes/ no*	9/7	24/46	5/102	9.67 [4.57, 21.73], <0.001
Respiratory: yes/no*	5/11	13/57	6/101	4.19 [1.84, 9.81], <0.001
Other: yes/no*	4/12	15/55	2/105	6.45 [2.73, 15.86], <0.001
Any Comorbidity: yes/no*	11/5	36/34	11/96	9.26 [4.77, 18.77], <0.001
Lymphocyte Count Prior to Covid-19 Infection ($10^{\wedge}9$/ microliter): Median (IQR), missing	2.05 (1.58, 2.83), 8	1.30 (0.80, 1.86), 24	1.27 (0.92, 1.72), 37	1.13 [0.83, 1.55], 0.426

4.2. Clinical features of hospitalised COVID-19 people with MS

In the case of 85 pwMS who were hospitalised, 54 (63.5%) were due to COVID-19, 7 (8.2%) for reasons associated with MS, 4 (4.7%) for social reasons (where the patient was unable to be supported at home) and 20 (23.5%) for 'other' or 'unknown' reasons. A median 9 days in hospital was recorded and this duration of stay was the same for all admissions regardless of survival. Levels of respiratory support for those in hospital were divided into low-dependency ('face mask' or 'nasal cannulae') and high-dependency ('high flow oxygen', 'non-invasive ventilation' or 'intubated and ventilated'), with a significant difference in survival rates between the two different intensity treatment levels (Fisher's Exact test; CI 0.03, 0.48, $p = 0.001$). Symptoms of infection associated with admission included respiratory problems (χ^2 13.17, df = 1, $p < 0.001$) and high temperature (χ^2 13.98, df = 1, $p < 0.001$).

Increasing age (t −8.88, df 159.71), male gender (χ^2 10.95, df = 1), having any comorbidity (χ^2 39.83, df = 1), increased disability (χ^2 54.17, df = 2) and progressive MS (χ^2 57.73, df = 1) were associated with being hospitalised ($p < 0.001$), while being on a DMT was associated with a lower likelihood of being admitted to hospital (χ^2 35.05, df = 1, $p < 0.001$).

4.3. Clinical features of people with ms dying as a result of COVID-19

One person with MS with COVID-19 died at home. Of those hospitalised, 15 out of 85 (17.7%) died; 11 of those (73.3%) had either 'critical' or 'severe' COVID-19 symptoms recorded compared to those who were admitted to hospital but survived (20%, $p < 0.01$)). 11 out of 15 (73.3%) of those who died in hospital had required some form of ventilatory support, compared to 31 out of 70 (44.3%) who were admitted but recovered. In the group that died, respiratory symptoms were found to be amongst the most significant (χ^2 3.74, df = 1, $p = 0.05$).

4.4. Outcome analysis: hospitalisation and death

Univariable ordinal logistic regression of serious events showed that male gender, older age, progressive disease, not being on active DMT treatment, and the presence of comorbidities were all significant (Table 1, $p < 0.01$), with age the most significant. In terms of disability, only severe disability was found to be significant. Lymphocyte count values prior to COVID-19 infection were not found to be significant.

When multivariable modeling was used there was high (>2.5) VIF for progressive MS type and EDSS. Standardised hypothesis tests found that these, as well as DMT treatments, the 'cardiac' and 'other' and 'any' comorbidity categories were all significantly associated with age at a level of $p < 0.01$; younger pwMS were more likely to be on a DMT, more likely to not have progressive disease, and to not have comorbidities. Respiratory comorbidities were associated with higher age at a level of $p = 0.02$ ($t - 2.48$, df = 29.46). Removing these due to the high levels of interaction, as well as lymphocyte counts, left only age and gender in the multivariable model, both showing significance at $p < 0.01$, Residual Deviance 261.71, AIC 269.71.

Treating the combined serious events as nominal categories, standardised hypothesis testing found significance in all factors at $p < 0.01$ except for lymphocyte counts prior to infection (Table 2, column 1). Post-hoc pairwise comparisons (Table 2, columns 2–4) found that significant differences were primarily found between the groups of those Alive, Hospitalised/Alive, Not Hospitalised, and Alive, Not Hospitalised/Deceased, Hospitalised, with no significant differences between the Alive, Hospitalised/Deceased, Hospitalised groups.

4.5. Differences between first and second wave

For this analysis, a further 21 pwMS from the confirmed COVID-19 group were excluded due to missing values for estimated infection date. The likelihood of being hospitalised due to COVID-19 decreased in the second wave ($\chi^2 = 35.40$, df = 1, $p < 0.001$), as did the likelihood of death (Fisher test; CI 0.02, 0.91, $p = 0.02$). As presented in Table 3, in the second wave pwMS were more likely to be younger (t −2.85, df 153), not have progressive MS ($\chi^2 = 8.50$, df = 1), have lower disability ($\chi^2 = 8.67$, df = 2) and more likely to be on a DMT ($\chi^2 = 5.03$, df = 1).

An ordinal logistic regression, again using age and gender as independent variables, was modeled on the first wave data, with age (OR 1.08, CI [1.04, 1.12]) and gender (OR 0.19, CI [0.06, 0.55]) both found to be significant at $p < 0.01$, Residual Deviance 109.18, AIC 117.18. This was able to predict outcomes in the first wave with an accuracy of 70.273% (CI 58.52%, 80.34%). Inaccurate predictions were a mixture of 13 better and 9 worse outcomes. Applying this model to the second wave found it to be 57.14% accurate (CI 46.75%, 67.10%), and 39/42 of the inaccurate predictions were for worse outcomes. Thus the model that fits the first wave predicted many more worse outcomes than occurred in the second wave. Repeating the process in reverse, using the second wave data for the model showed age (OR 1.11, CI [1.06, 1.17], $p < 0.01$) and gender (OR 0.29, CI [0.09, 0.94], $p = 0.04$) were again significant with an accuracy of 83.67% (CI 74.84%, 90.37%), Residual Deviance 86.46, AIC 94.46. 13/16 of the incorrect predictions were for better outcomes than happened. Applying this model to the first wave data gave an accuracy of 55.41 (CI 43.49%, 66.98%) and all predicted

Table 2
Standard hypothesis testing for nominal serious event categories, with post-hoc pairwise results for significant variables. Tests were conducted using Chi Squared and analysis of variance (ANOVA). Kruskal-Wallis test was substituted for ANOVA where results were non-normal, and Fisher's Exact test was substituted for Chi Squared where expected values were small. Post-hoc pairwise comparisons using Bonferroni adjustment were calculated for factors achieving statistical significance.

Characteristic	n	Standard hypothesis test: p-value	Post-hoc pairwise association tests, using Bonferroni adjustment: p-value		
			Alive, Not Hospitalised/Alive, Hospitalised	Alive, Hospitalised/ Deceased, Hospitalised	Alive, Not Hospitalised/ Deceased, Hospitalised
Gender: Female/Male, missing	134/59, 0	0.001	0.002	1.000	0.153
Age (Years) Mean, Standard Deviation, missing	50.75, 14.90, 0	<0.001	<0.001	0.200	<0.001
MS Type: progressive/not progressive, missing	74/112, 7	<0.001	<0.001	0.293	<0.001
EDSS Group: mild/moderate/severe, missing	60/38/ 74, 21	<0.001	<0.001	0.708	<0.001
DMT: yes/no, missing	107/80, 6	<0.001	<0.001	0.381	<0.001
Comorbidities:	38/155	<0.001	<0.001	0.459	<0.001
Cardiac: yes/no	24/169	0.002	0.034	0.930	0.017
Respiratory: yes/no	21/172	<0.001	<0.001	1.000	0.008
Other: yes/no	58/135	<0.001	<0.001	0.810	<0.001
Any Comorbidity: yes/no					
Lymphocyte Count Prior to Covid-19 Infection (10^9/microlitre), Mean, Standard Deviation, missing	1.58, 1.14, 69	0.134	–	–	–

Table 3
Population demographics and clinical features of the first ($n = 74$) and second waves ($n = 98$). Tests were conducted using Chi Squared and analysis of variance (ANOVA). Kruskal-Wallis test was substituted for ANOVA where results were non-normal, and Fisher's Exact test was substituted for Chi Squared where expected values were small.

Characteristic	First wave $n = 74$	Second Wave $n = 98$	Standard Hypothesis test: p-value
Gender: Female/Male, missing	48/26, 0	72/26, 0	0.294
Age (Years): Median (IQR), missing	54 (44, 64), 0	46 (37, 54), 0	0.005
MS Type: progressive/not progressive, missing	36/33, 5	28/70, 0	0.003
EDSS Group: mild/ moderate/severe, missing	18/10/35, 11	38/24/29, 7	0.013
DMT: yes/no, missing	35/35, 4	67/31, 0	0.025
Hospitalised: yes/no, missing	51/23, 0	22/76, 0	<0.001
Deceased: yes/no, missing	8/66, 0	2/96, 0	0.020

outcomes were better than the observed outcomes: 25 predictions were for the person would be alive without needing hospitalisation when in reality they were hospitalised, 4 predictions were for the person being alive but hospitalised when in reality they died, and 4 predictions were for the person being alive and not hospitalised when in reality they died.

5. Discussion

We present an overview of COVID-19 in pwMS from England, Wales and Northern Ireland, showing that the features associated with poor outcome in confirmed COVID-19 infection are similar to other non-MS populations reported around the world. We found a range of MS and non-MS factors appeared to be relevant to COVID-19 outcome, but in multivariable analysis only older age and male gender remained as significant predictors of poor outcome. We also demonstrated that these factors were associated with hospitalisation, but once hospitalised, none were associated with mortality. This implies that once in hospital factors, not quantified here, are predictive of mortality.

Our findings are consistent with our community-based self-reported study in the UK where there were fewer pwMS self-reporting as being hospitalised (Evangelou et al., 2020), and with other Register-based studies (Louapre et al., 2020), which also found that pwMS on a DMT were not at an increased risk of a poor outcome, but contrasts with international data on increased risks with some DMTs (Simpson-Yap et al., 2021). However, in common with our findings they did not find that DMTs were associated with a higher mortality (Simpson-Yap et al., 2021). This is perhaps because those on DMTs are generally younger and have lower levels of disability than those not on DMTs, would be less at risk of serious COVID outcomes and were also advised to self-isolate (IfG 2021b). Thus, it seems likely in the UK that the behavior of people on DMTs is potentially an important factor.

Reassuringly, we see that the outlook for COVID-19 in pwMS has improved in the second wave, as we observed younger, less progressive people having improved survival rates, in keeping with UK and other international results (IfG, 2021b; Griffin, 2020; James et al., 2021). Age and gender provided a better fit for the second wave model than the first, suggesting that the higher hospitalisation and mortality in the first wave may be attributed to other factors not accounted for in this data. Certainly, during the first wave there remains a concern about how decisions regarding treatment were made for those at-risk populations e.g. those above a certain age but also those with prior disabilities. These decisions were managed more cohesively following guidance for the second wave (Williamson et al., 2021; IfG, 2021).

Limitations of our study largely relate to the fact that the data capture tool was devised at the outset of the pandemic; the understanding of the COVID-19 infection has evolved over the course of the pandemic. As a result, we did not capture ethnicity (Garjani et al., 2021) or body mass index (Razieh et al., 2020), which have subsequently been shown to be factors associated with increased mortality.

Another factor was the limited availability of PCR testing in the first few weeks of the pandemic; this was eventually resolved through wider more effective testing, but it may have affected our analysis as several pwMS were excluded due to inconclusive COVID-19 status.

As with all studies we have to be mindful of reporting bias (McGauran et al., 2010), particularly in a study such as this where data is 'volunteered' by interested clinicians. Despite this, 46 different sites across England, Northern Ireland and Wales contributed data to this study across all time points. Reporting bias may also mean the most serious cases were reported, and milder community cases more likely to be missed. Additionally, pwMS on DMTs were potentially over-reported due to having a higher likelihood of being reviewed by neurologists due to their treatment regimen but ultimately the sample size as with other studies may have limited our ability to draw conclusions on DMTS.

6. Conclusion

Increasing age was the most significant factor for risk of hospitalisation and mortality in pwMS infected with COVID-19. Male gender, increasing disability, progressive MS, and the presence of comorbidities were also found to be associated with a higher risk whereas being on a disease modifying therapy was associated with a lower risk of hospitalisation and mortality. Once in hospital none of these factors were predictive of mortality.

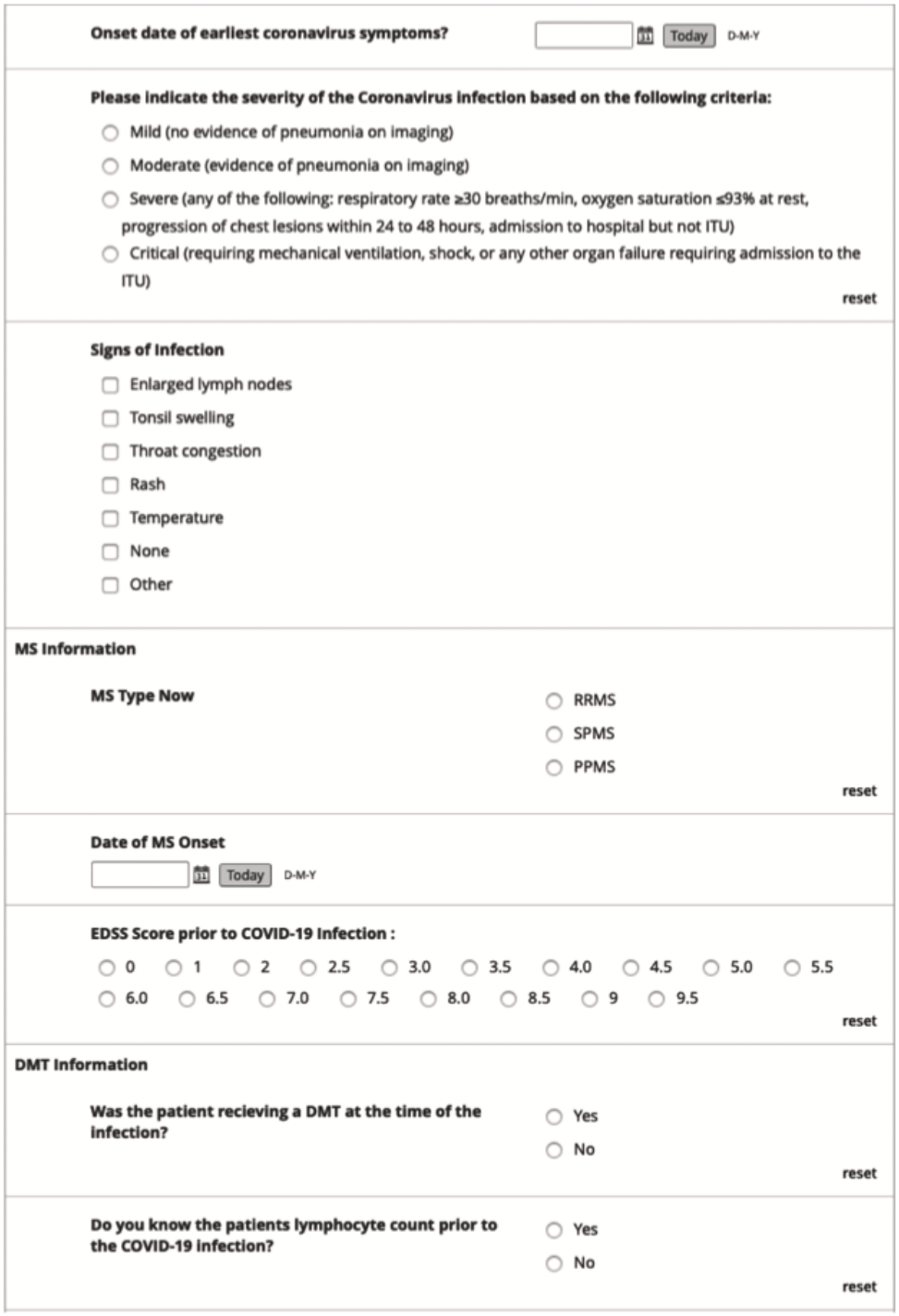

Fig. A1. Appendix 1: Example electronic case return form section.

CRediT authorship contribution statement

RM Middleton: Conceptualization, Writing – original draft, Methodology, Resources. **EM Craig:** Methodology, Software, Data curation, Formal analysis. **WJ Rodgers:** Methodology, Formal analysis. **K Tuite-Dalton:** Validation. **A Garjani:** Writing – review & editing, Data curation. **N Evangelou:** Writing – review & editing, Data curation. **R das Nair:** Writing – review & editing, Data curation. **R Hunter:** Writing – review & editing, Data curation. **EC Tallantyre:** Writing – review & editing, Data curation. **M Cauchi:** Data curation. **C Cairn:** Data curation. **D Paling:** Data curation. **S Fuller:** Data curation. **G McDonnell:** Data curation. **K Petheram:** Data curation. **B Liu:** Data curation. **U Nock:** Data curation. **G Ingram:** Data curation. **W Brownlee:** Writing – review & editing, Data curation. **J Taylor:** Data curation. **R Nicholas:** Writing – review & editing, Methodology, Supervision.

Conflicts of Interest

RMM, EMC, WJR, and KT-D, as part of the UK MS Register, have received grants from the MS Society. RdN has received research funding from the UK MS Society, National Institute for Health Research, & Medical Research Council, as well as funding (speakers' bureau) from Novartis, Biogen, and Merck. ECT had received honoraria, speaker fees or travel expenses for educational meetings from Biogen, Merck, Novartis, Roche and Takeda, unrelated to this work. DP is local principal investigator for commercial trials funded by Novartis and Janssen Pharmaceuticals, reports an investigator grant from Sanofi Genzyme, and reports advisory boards/consultancy and speakers fees from Biogen, Celgene, Janssen, MedDay, Merck, Novartis and Roche. WB received honoraria for educational activities and/or participated in advisory boards for Biogen, Celgene, Mylan; Novartis, Roche, Sanofi. RN reports support from advisory boards and travel expenses from Novartis, Roche and Biogen. He has grant support from the UK MS Society and is a member of a NICE HTA committee.This study was funded by Multiple Sclerosis Society (https://doi.org/10.13039/501100000381) and grant number: MSREG-001The UK MS Register has ethical approval from South-West Central Bristol Research Ethics Committee (16/SW/0194).

Appendix

Fig. A1

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Conclusions

An important finding in this paper was that the data that we gathered aligned with earlier patient-supplied data from the UKMSR, and with that on the impact of DMT therapy on mortality in large international studies looking at DMTs and COVID-19 (Simpson-Yap et al., 2021). This was amongst the first papers in MS to look at changing population behaviour affecting hospitalisation and outcomes over waves of COVID-19, and showed that pwMS did not seem to be of increased risk of a poor outcome due to MS and COVID-19.

This paper added to the wealth of data that had been captured by the UKMSR over the course of the pandemic. It reinforced the results from the patient reported outcomes that we had been capturing (Evangelou et al., 2020), namely that there were fewer people with MS being hospitalised with COVID-19 infection and that being on a DMT was not a predictor of a poor outcome.

An especially innovative feature of this paper that many other rare disease data collection exercises would have struggled to reproduce was the analysis between waves of the pandemic. The rapid turn around in the deployment of the clinical instrument from the outset of the pandemic allowed us to look for any differences between the severity of illness of the patients being admitted and then in their overall outcomes. Older males had the worst survival rates overall – though this was in common with most other COVID-19 studies. The second wave of the pandemic showed improved survival rates and fewer hospitalisations. Being on a DMT was linked to a reduced likelihood of hospitalisation.

This last point is particularly interesting and is related to work we had submitted as part of the international effort (Simpson-Yap et al., 2021). This had illustrated that most DMTs were safe to use in the presence of COVID-19 but that there was an increased risk of mortality for those patients receiving Ocrelizumab/Rituximab. It is worth noting that this international effort from 28 countries at the height of the pandemic only had data on 657 pwMS with suspected or confirmed COVID-19. The data in this paper is from 193 patients. Being able to concur with an international study specifically designed to look at DMT risk shows the power of the UK MS Register and its ability to publish data of international significance. The fact that our data contributed to the international study also shows the quality and value of the data collected by the UKMSR in an international context.

Fundamentally, this paper represents the fruition of many of my aspirations for the UK MS Register at its outset. It corroborated patient supplied data as being accurate, it engaged with clinicians across the country, and they were able to supply a relevant dataset. The data captured from it were of national significance and that data was replicable in an international cohort. The UKMS Register was now recognised both nationally and internationally as a valid repository of research data for internal researchers, for our clinical partners, and for external researchers to make use of subject to governance.

The ability to achieve all this whilst in the middle of a pandemic was a testament to the underlying design, and the commitment of the participants and their clinicians.

Chapter 10: Discussion

Summary

In this thesis I have related my experiences of designing, implementing, and deploying the United Kingdom Multiple Sclerosis Register. The Register is unique in its design of capturing longitudinal data directly from people with MS and from clinicians and then linking those data. The intention that those data could then be anonymised and made available for any appropriate researchers, subject to funding and governance.

My fundamental design goal for the Register was that it be an entirely electronic platform, capable of capturing research quality data from real-world sources in a secure and trustworthy fashion that would be acceptable to clinicians, people with MS and other stakeholders. The aim was that this model would generate research, as well as potentially be useful to other disease areas, or other MS Researchers around the world.

To achieve these goals, I have highlighted papers here that I felt were crucial in showing the development and implementation of the MS Register – from concept, through introduction, to established working Register – with examples of all aspects of the UKMSR's impact. As of March 2023, the Register has 24,822 online participants, 13,705 clinical minimum datasets from the NHS, and 4,711 patients linked between the two domains. In just the repeat 'core' outcome measures (MSIS/EQ5D/MSWS/FSS/HADS) we have 451,527 completed questionnaires; with hundreds of thousands of additional, more intermittent, surveys linkable.

As stated in the introduction, there was initially a serious lack of data about multiple sclerosis in the UK and my work in developing the Register as a platform has made a significant impact on MS research. The breadth of topics covered by the papers featured in this thesis go some way to illustrating some potential uses of the Register platform and its flexibility.

In Chapter 2 of this work, I highlight the needs and expectations of people with MS, for what would be a minimally functional 'register'. It needed to be a useful and trustworthy repository of their data, but it also set the precedent of involving people with MS in all aspects of the Register's working groups and design. Chapter 2 illustrates the working Register, demonstrating people with MS coming at scale to the platform, securely logging in and contributing useful patient reported outcome measures.

Chapters 2 and 3 combined show the desire of people with MS to co-create and build such a repository of data. In this paper I report on the 5,819 pwMS that contributed to this point and established that this demand existed beyond the limited number of people that were able to take part in the focus groups in Chapter 1.

In Chapter 4, the utility of data from the SAIL databank is demonstrated. Being unable to link records from the Register was unfortunate but unavoidable at this early stage; however, creating an algorithm to identify pwMS within SAIL would prove extremely useful later in the development of the Register, and this paper laid the groundwork for later linkage of Register data within SAIL.

The paper in Chapter 5 was crucial to acceptance of the UKMSR, particularly amongst clinical colleagues. The validation that the online participants behaved similarly to a cohort of clinically diagnosed patients with MS was of immense benefit to the UKMSR, and to other researchers who were beginning to make use of the MS Register platform.

In Chapter 6, I illustrate the ability to use the MS Register to recruit patients for the capture of innovative datasets – cognition in this case – and link those data to pre-existing records within the MS Register. It also demonstrated the UKMSR's expansive ability to be able to deploy instrumentation such as this to an audience who were keen to take part in more comprehensive PROs. This data could also be of immense use to clinicians and potentially trialists as part of forming a more holistic picture of an individual's MS, beyond the standard EDSS score.

Chapter 7 returns to the expectations of pwMS for an MS Register, and fundamentally how the existence of the UKMSR had moved the goalposts for what people expected. The desire for more comprehensive data being returned to participants was one that I was happy to design into later iterations of the platform. There was a conclusive desire for people to be better informed about their disease, to view it in an accessible way and to potentially have this data shared with their clinician, which would change the UKMSR going forward.

In Chapter 8, the consequences of the COVID-19 pandemic came to the fore. The paper was important for several reasons. It showed the ability of the platform to rapidly pivot to collect newly-essential data in the face of a global emergency, a continued desire from people with MS to supply that information, and that the UKMSR could produce timely, peer-reviewed evidence that continuing to take current DMTs was safe. This, combined with the paper in Chapter 9, shows the accomplishment of my goals that the Register be comprehensive (across clinical and PRO data); rigorous in its analysis; equitable in including as many pwMS and their clinicians as could provide reliable data; and open in the publication of research. Looking at COVID-19 in the clinical data allowed us to examine more severe infection outcomes and confirm that the clinical evidence was similar to that of the patient reported ones – as well as demonstrate that the mortality and morbidity of people with MS improved over at least one subsequent wave of the pandemic.

Discussion

Collection of any form of research data is not something that occurs overnight; it is a dedicated effort involving collaboration from large numbers of people, information platform architecture, and funding to bring these elements together. Though the call to create an MS Register was a funded one from the MS Society in 2010, the method of how this was to be done was entirely open-ended. Indeed, competing bids at the time were focussed on more traditional approaches, such as starting at a hospital with an already well-defined and purely clinical population, and then expanding to other centres with similar datasets.

In many disease areas this approach works well – where there is existing high-quality retrospective data, where consent to use this data for research has been sought from the participants, or where there is funding to begin this procedure from the initiation of the research project, clinical audit, or notifiable disease. This kind of approach has worked well in conditions such as in rheumatology (Silman, 2003) where the cost and potential side

effects of the DMTs were of particular interest, or heart disease (Myocardial Ischaemia National Audit Project) (Birkhead, 2000) where there is a sufficiently urgent case. In rare diseases with uncertain aetiology such as multiple sclerosis this is a more difficult path to follow. As stated in the introduction, a register is distinct from a database: registers "*contain uniform information about individual persons collected in a systematic and comprehensive way in order to serve a predetermined purpose*" (Brooke and Organization, 1974), but "registries" can refer to both programs that collect and store data and the records that are so created. This makes the data in a register much more holistic than that contained within a trial or a database, and the definition of its predetermined purpose even more essential. The UK MS Register was designed to be the pre-eminent real-world data collection about people with MS in the United Kingdom. The outcome data that is routinely and longitudinally collected into the MS Register represents this purpose but is deliberately open-ended; the intention to assemble new datasets in future about those 'individual persons' only adds to the value of the Register. Chapter 3 shows those patient reported outcomes, while Chapter 5 shows their overlaps with clinical data. Chapter 6 shows the first 'new' dataset, a cognitive one added to this collection, while the COVID-19 papers expand this further. More recently, the Register has begun to collect limited imaging data in the form of MRI scans and some genetic data (Vickaryous et al., 2020) and this effort is being increased further as part of the ADAMS study ("ADAMS - Home," n.d.), which is attempting to capture more ethnically diverse genetic data from people with MS.

The UKMSR has become a notable, ongoing accumulation of real-world data, fitting its purpose of being a platform to which novel data collection instruments can be added, whilst focussing on a core data set of regularly collected responses from individuals with the disease and their clinicians. My work here illustrates the scale of this platform and *some* of the uses to which the data can be put. This is only part of the picture, however, as the platform was also designed to enable others to do wide-ranging, impactful longitudinal research and this has begun to take place.

Anecdotally, I would estimate that it takes ten years for register data to become useful. This is especially true in rare disease registers where data collection can be sparse coming from a smaller population and can take time to accrete value. Looking at the other well-established MS disease registers, their 'output' in terms of initial publications is primarily methodological or cross-sectional examples of particular data collection periods ((Watson, 2005), (Mehta, 2010)). This is unsurprising when so many publications note that one of the core factors in a disease register's success is the capture of truly longitudinal data beyond the three to five years of a traditional clinical trial (Hillert and Stawiarz, 2015), (EMA, n.d.) (Butzkueven, n.d.). This shift in UKMSR output from methodological or fixed instances of temporal research into the truly longitudinal is best demonstrated by (Rodgers et al., 2021) paper on *The impact of smoking cessation on multiple sclerosis disease progression*. The paper takes the core MS Register instruments, from participants who submitted in a six-year period, stratifies them by smoker, ex-smoker and never smoker and is able to carry out a comprehensive longitudinal analysis that illustrates one clear result – smokers with multiple sclerosis develop worse disability than those who never smoked, when measured over the same time period. More importantly, however, stopping smoking at any time can show almost immediate benefits, with the disability levels of those that stop trending towards those who have never smoked in a relatively short period of time.

This research has the potential to make a large public health impact and has been adopted by several MS clinics as part of their stop smoking programs. Beyond the increase in the UKMSR's research profile from being featured in a high impact factor journal, this is an exciting demonstration of the real benefits of disease registers, and of PROs to clinical teams, not just in a more abstract manner to researchers. Without the data having been systematically supplied to the platform by the NHS and participants, and without that data being accessible to researchers from across the UK and Europe, this important paper would never have been produced. This is the truest illustration of the UKMSR as a platform: reliable and validated longitudinal data captured in a systematic way and then made accessible to appropriately qualified researchers with anonymisation and safeguards in place. The process is reproducible and transparent from collection to publication.

This, while being a fantastic project to highlight, represents one of many that have been enabled by the MS Register platform since its inception in 2011. By 2014 we had appeared in a landmark publication on the state of European MS Registers (Flachenecker et al., 2014). Two years later, the first publication based on a dedicated unique survey specified by third-party researchers and linked to existing MS Register data was featured (Baker et al., 2016) and these have been followed by 32 subsequent papers from MS researchers across the world. Ten projects are currently ongoing as of March 2023. The papers generated by third-party researchers using UKMSR data can be seen in Appendix 1; these are in addition to the publications led by the UKMSR, some of which form the basis of this thesis. Appendix 2 is a snapshot of the interactions of the UKMSR for 2022, provided here in order to illustrate its position in UK MS Research.

Other MS Registers

As stated in Chapter 1 there are a number of MS Registers extant in the world. The majority of these have a nation-based focus; Swedish, Norwegian, Danish, German et al, and at least at the time of the UKMSRs launch, an entirely clinical basis for collecting data - with the exception of the American NARCOMS register. MSBase, a register designed for taking a minimum clinical dataset longitudinally from any participating clinical site (with appropriate permission) had a more global focus. It is interesting to note how successful all of these registers have become in terms of scientific output and funding, and how they have also moved towards more collaboration and capture of PROs. Multiple Sclerosis is a rare disease and the amount of high-quality data that must be collected to draw robust conclusions is similarly high. The research we have been able to carry out – and enable, with UKMSR has multiple examples of high-quality research, enabled by the capture of 'big data' from a variety of sources. This was taken to an even higher level during the pandemic when collaboration with other Registers on the issues of DMT in light of a COVID infection (Simpson-Yap et al., 2021) became essential due to scale. Of note, this collaboration was with many of the registers previously mentioned (Sweden, Germany, NARCOMS and MSBase).

Ethics between countries differ as do rules for data sharing. The drivers for collecting observational data between registers are common with a small amount of overlap but each register is capable of collecting these data to service their own ends and can come together when needed for bigger research projects. The concept of registers being complementary

and collaborative in this way can only be a good direction of travel for MS Research.

Another factor that influences this, and was discussed in Chapter 6 is the shift by regulators including the European Medical Agency (EMA), the Food and Drug Administration (FDA) and the Medicines Health Regulatory Agency (MHRA) in the UK looking for patient reported outcomes in submissions for approvals for medications. Those registers that have not collected these types of outcomes are now making moves to do so and are referring to the UKMSR as a leader in the field. Again, this can only be good for all registers and ultimately patients - whose voice will be more strongly heard.

Limitations

All of the papers highlighted in this thesis have clearly set limitations and it is important to note that the UKMSR is also not without its own limitations. The first is that it does not cover 100% of the UK population. There are a number of reasons for this – firstly, the UKMSR relies upon both individuals and NHS sites to provide data, and data capture from both can be resource- and time-dependent. Secondly, the existence of a separate Scottish MS Register (Kearns et al., 2019) and other databases such as OPTIMISE (Dobson et al., 2021) which, to some degree, compete for the same or similar resources and inclination from pwMS and NHS sites, have caused a certain amount of dilution. However, these other projects have different purposes, with the Scottish Register serving entirely as an incidence register and OPTIMISE being focussed purely on capture of DMT data. These initiatives therefore collect different data to the UKMSR and indeed we have worked with the principal investigators of both projects to ensure that there is as little repetition of data collection as possible, and we remain open to further collaborations in the future.

This leaves the UKMSR as the only well-established nationwide MS prevalence register, and with almost 20% of the estimated MS population of the UK it is sufficiently powered to answer appropriate research questions – as evidenced in the international efforts that the UKMSR has contributed to.

Something that could be seen as a limitation is the duration of the study itself. There are relatively few online participants who have completed all of the required instruments over the 12 years of the Register's existence (640 as of March 2023). We have been able to demonstrate in other papers that participants do return for a median period of 2.5 years. This in itself represents a reasonable time commitment to the project but also shows the strength in continual recruitment and gives us opportunities to compare these new participants to those from previous recruitment waves. Thus, we can view the change in living with MS in the UK over subsequent years, through pandemics, and in populations with different treatments available to them.

A further factor that should be acknowledged is bias. There are many potential sources of bias in an observational study such as the UKMSR. Ascertainment or selection bias is where the population recruited are different from the actual population that you wish to study (Grimes and Schulz, 2002). This is clearly a danger in an online only patient portal as only those people with computers and sufficient ability are able to take part. We did attempt to offset this as much as possible through clinical recruitment where no participant input was required and by providing a field to indicate where a survey was being completed by a

friend/carer rather than the participant themselves. Though the fact remains it leads to a skewed population.

A second type of bias that the UKMSR portal is subject to is recall bias - always a potential factor in epidemiological or medical research (Althubaiti, 2016) but It is a particular concern in people with MS who may experience issues with long and short term memory, which can be confounded further with fatigue. We can partially control for this within the Register by linking portal and clinical records together. The work in Chapter 5 illustrates the accuracy of this approach to some extent, but more work is needed. Future publications will look to more subgroup analysis to better quantify the impact of this effect.

A potentially major limitation of establishing any disease register is cost; the primary costs being technology and staff. Longitudinal registers are, by necessity, long-term efforts. The setup costs of software and hardware needed to run the infrastructure of a register can be significant (depending on scale) but are essentially one-time costs. The ongoing costs are substantial, with requirements to write code for websites, databases, analysis and papers for peer-reviewed journals. There is a need to maintain and market the online platform and in parallel create a secure system for clinical data, build relationships with participants and NHS staff, and absorb input from a variety of stakeholders across all areas that the Register covers. These costs for internal staff that are dedicated to the project can run to hundreds of thousands of pounds annually, making this a significant consideration.

Conclusions

The papers discussed in this thesis illustrate the genesis of the UK MS Register. All of them were important building blocks in the construction of a platform that would enable people with MS to contribute clinically meaningful data and have researchers from across the world access it in a secure, privacy-protecting way. People with MS have been involved at every stage of the MS Register development and this has served as a huge spur to its acceptance across all of its stakeholders and massively contributed to its success. This document, and the others referenced as outputs of the MS Register, illustrate the value of the platform. This thesis and the papers it contains may serve as a blueprint for other disease areas, particularly where capturing the patient's 'voice' is considered as important as clinical opinion. Bringing these voices together can provide meaningful opportunities for research that are relevant to all with long-term conditions; such an initiative can strive to improve treatments, and better understand individuals and their carers. We are all 'patients' at some point in our lives and internal narratives of our conditions, though subject to our own biases and senses, give a unique perspective to research. Combining all of these perspectives through linked data, with the ability to easily introduce new elements, gives us unparalleled opportunities.

The platform that I architected, designed and have outlined the evolution of within this thesis is flourishing. It has enabled the research that it was commissioned for in 2010, whilst also being flexible enough to adapt to the rapidly changing world of research. It serves more stakeholders from across the world each year in the creation of meaningful impactful research that can make a difference to the lives of people with MS.

Future Work

For the future, I foresee a number of applications and enhancements to the current MS Register and its outputs, both from internal usage and for external researchers.

Cognition

The next iteration of the CoRe development has been deployed via Apple 'test-flight' directly to participants of the web portal of the MS Register. This version allows testing on smartphones as well as iPads, has two different symbol sets to choose from and includes a voice response functionality. This version has only just started testing with about 250 responses but I hope that the CoRe instrument becomes a routine, robust assessment metric in MS Care and research.

The initial steps in this work are due to be presented at the American Association of Neurologists conference in Boston in April 2023. Home-based measurement of cognition could be immensely useful to pwMS and researchers as part of a more significant understanding of this element of the disease. This app-based data capture is being supplemented with data from the ‘Cognitron’ instrument, a questionnaire developed by researchers at Imperial College London and deployed longitudinally on the UKMSR. Initial signs from this work are encouraging and have been featured as a poster at the Association of British Neurologists (ABN) conference (Lerede et al., 2022) with a manuscript in preparation for peer review. This work is currently also being considered for international research with the Swedish MS Register. Further work in this area can only be beneficial to patients.

Recruitment to Clinical Trials

This was a stated goal of the pwMS that took part in the paper in Chapter 2; that a register could highlight clinical trials to participants who met stated eligibility criteria, and this was built into the ethical approval of the Register from the outset. This has already occurred in a limited way with information to participants being given about the CHARIOT MS Trial. The newer initiative to recruit to OCTOPUS (“Register Your Interest,” n.d.) a multi-arm multi-stage innovative drug trial in MS – is being entirely run via the UK MS Register, and 916 people have been found to be eligible for telephone screening as of March 2023. The ability to recruit so many people at the very earliest stages of a clinical trial could be a significant factor in its overall operation and results.

More than this we are looking at carrying out ‘virtual trials’ within the MS Register. The purpose of OCTOPUS is to investigate the repurposing of medications not originally designed for MS, and observe if there are any differences in progression. The MS Register is in an ideal position to model these drugs and factors within its existing populations and a talk on this has also been accepted at the American Association of Neurologists (AAN) conference for 2023, with a paper to follow. This builds directly from participant expectations and uses the power to expand the platform with novel datasets, as demonstrated in Chapters 6, 8 and 9.

Development of early career researchers

We realise the value that having linked data of the various types stored within the UK MS

Register's TRE represent. It is difficult to get access to real or synthetic data on which early career researchers (ECR) can develop their skills or be given the opportunity to work with for their own research ideas. We therefore held a 'Datathon' in June 2022 where 25 ECR were given access to a 'cut' of the data within the Register environment. This process led to the generation of five academic posters that were shown at the MS Frontiers 2022 conference, with the winning group submitting a paper to the British Medical Journal (BMJ) open (currently under review). Given the success of the Datathon, it will be held again in 2023, with the intention of making it an annual event for the foreseeable future.

We are also currently in the early stages of designing a prepared, research-ready dataset for master's students who want to conduct analyses as part of their degree but are not yet as familiar with analytical tools as the more experienced researchers that the UKMSR usually caters for.

These projects are designed to enhance the skills of the next generation of researchers, raise awareness of the Register, and potentially open the data up to new questions and methods of analysis in MS research.

New Analytical Approaches : Machine Learning and Meta-Analysis

Having a multi-faceted data model also represents a huge opportunity in the federated analysis and machine learning spaces. The UKMSR has already carried out a number of projects in this area, and is laying the groundwork for more.

First and foremost is a project carried out across Sweden, Germany, Denmark and Czechia, where a composite data dictionary from all registers was defined and meta queries carried out. One publication from this work has been produced already (Forsberg et al., 2023) and another is pending review with the Journal of Neurology, Neurosurgery and Psychology.

Secondly, the opportunities for other types of machine learning on free-text data, submitted by pwMS to the portal as comments and from the NHS as outpatient letters, is a potential treasure trove of meaningful data that could be utilised with the correct tools and methods. The UKMSR environment is ideal for this and a number of academic posters (Middleton et al., 2022) have been produced showing the initial forays into this valuable resource. For machine learning to be effective, scale is required; this is already possible on larger repositories of data such as HES and SAIL, but it has taken time for the UKMSR to reach this stage. Given the sheer number of PROs and clinical datasets the Register now holds, and toolsets we have available, it is increasingly becoming a realistic and significant opportunity for MS research.

Reporting Datasets and data standards

As stated in the methods section, I am keen that the MS Register becomes even more aligned with standards for reporting and storage of data. The COVID and CoRE papers featured in this thesis were submitted with STROBE checklists; data from subsequent SAIL papers will also complete the RECORD checklist as part of publication requirements. Data from the ongoing initiatives looking at Natural Language Processing techniques for free text is being processed and linked to SNOMED as part of its function, to ensure that it is easily consumable and linkable to other MS Register data and on to other data sources.

Additionally I am investigating converting the UKMSR datasets to the Observational Health Data Sciences and Informatics (OHDSI) and their Observational Medical Outcomes Partnership (OMOP) common data model (Hripcsak et al., 2021). This open-source initiative to standardise health data science models utilises SNOMED and seems to align with a useful direction of travel for European registers and other large collections of health-related data. It is not a straightforward model to implement on such a varied data collection as the UKMSR however, so we are at a very early stage of this investigation whilst we await the maturation of some of the toolsets.

Costs

As I have stated in limitations the funding required to set up and maintain a disease register can be significant and ongoing; however, this can be offset by a number of factors. There is a quantifiable output in research activity and, put bluntly, it costs money to carry out research, employment, papers writing and to publish findings. There are efficiencies in the data being collected in one place and being able to link these data to diverse datasets actually leads to cost savings for funders as they don't need to commission multiple research strands that may be unrelated. The value in the data that is already collected is significant, but new data allowing new discoveries can be added or linked to with minimal additional cost.

Having this data collected in this way, and providing a TRE allows the Register to charge others to have access to this data. The costs that can be recovered here are also potentially significant and a sliding scale model can be applied where early career researchers can be only charged a notional administrative fee, all the way up to a pharmaceutical company being charged significant amounts of money for a single study. Processes to allow this have to be transparent to all, and bounded with excellent governance, allowing research to be done by all stakeholders at a price that is suitable for them. This has been the case with the MS Register; researchers applying to use the platform are charged varying rates depending on whether they are a student, a research group with their own funding, the NHS or the pharmaceutical industry.

Lastly, the technology expertise and staff needed to develop and run a register such as the MS Register, allows for economies of scale when the ‘next’ register applies to do something similar. Simply put the lessons, and some of the ‘infrastructure’ investment that has been made to develop the UKMSR can be applied to other diseases in a relatively straightforward way.

This thesis shows a potential pathway for others that may wish to develop an electronic disease register and it discusses many of the aspects that researchers may wish to consider in their establishment. Hopefully, it is able to provide guidance on diverse topics around the importance of involving people with the disease in their development, through the selection of data items and the incredible value in having linkable data with clear metadata so that other researchers can benefit from that data collection.

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Acronyms

Acronym	Expansion
AAN	American Association of Neurologists
ABN	Association of British Neurologists
ASP	Active Server Pages
CI	Confidence Interval
CSF	Cerebrospinal Fluid
DMT	Disease Modifying Therapies
eCRF	electronic Case Return Form
ECR	Early Career Researchers
EHR	Electronic Health Record
EQ5D	EuroQol Five Dimensions of living scale
FAIR	Findable, Accessible, Interoperable and Reusable
GPRD	General Practice Research Database
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
IIS	Internet Information Service
ICD-10	International Classification of Diseases Version 10
LSOA	Lower Super Output Area
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale 29
NHS	National Health Service
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes

	Partnership
ONS	Office of National Statistics
PEDW	Patient Episode Data Wales
PCR	Polymerase Chain Reaction
PPI	Patient/Participant and Public Involvement
PPMS	Primary Progressive Multiple Sclerosis
PROs	Patient Reported Outcomes
pwMS	people with Multiple Sclerosis
RECORD	REporting of studies Conducted using Observational Routinely collected Data
RCT	Randomised Clinical Trial
RRMS	Relapsing Remitting Multiple Sclerosis
SD	Standard Deviation
SPMS	Secondary Progressive Multiple Sclerosis
STROBE	Strengthening the Reporting of Studies in Epidemiology
TRE	Trusted Research Environment
UKMSR	United Kingdom Multiple Sclerosis Register

Appendix 1: Papers from third-party researchers using the UK MS Register

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Appendix 2: UKMSR 2022 – A Snapshot