Title Page

Title - The contemporary role of MRI in the monitoring and management of people with multiple sclerosis in the UK

Corresponding author – Helen L. Ford, Address: Department of Adult Neurology, Leeds General Infirmary, Leeds, UK, LS1 3EX. E-mail: helen.ford17@nhs.net Telephone: +44 01133922244. Fax: +44 01133922244

Authors, affiliations and contacts –

1. Linford Fernandes, Leeds Teaching Hospitals NHS Trust, Leeds, UK
2. Christopher Martin Allen, Queen's Medical Centre, Nottingham, UK
3. Thomas Williams, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
4. Emma Tallantyre, University Hospital of Wales, Cardiff, UK
5. Nikos Evangelou, University of Nottingham, Nottingham, UK
6. Jeremy Chataway, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
7. Helen L. Ford, Leeds Teaching Hospitals NHS Trust, Leeds, UK

on behalf of the UK MS Trials and Registries Consortium investigators:

8. Ala Abuown, Imperial College Healthcare NHS Trust
9. Michael Andrews, Barts Health NHS Trust, UK
10. Tarunya Arun, University Hospitals of Coventry and Warwickshire, Coventry, UK
11. Gavin Brittain, Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
12. William Brown, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
13. Alasdair Coles, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

14. Ibrahim Djoukhadar, Manchester Centre for Clinical Neurosciences, Neuroradiology Department, Salford Royal NHS Foundation Trust, Salford, UK
15. Anisha Doshi, Queen Square MS Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, London, UK
16. Amar Elsaddig, Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK
17. Peter Fernandes, University of Edinburgh, Edinburgh, UK
18. Leonora Fisniku, University Hospitals Sussex NHS Foundation Trust
19. Shayna Franzetti, Sunderland Royal Hospital
20. Ian Galea, Clinical Neurosciences, Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
21. Orla Gray, Ulster Hospital, South Eastern Health and Social Care Trust, Belfast, UK
22. Marc Hardwick, Wessex Neurosciences Centre, University Hospital Southampton, UK
23. Stella Hughes, Department of Neurology, Belfast Health & Social Care Trust, Belfast, UK
24. Gillian Ingram, Swansea Bay University Health Board, Swansea, UK
25. Seema Kalra, Royal Stoke MS Centre, University Hospital North Midlands NHS Trust, Stoke-on-Trent, UK
26. Fiona Kennedy, Department of Neurology, Belfast Health & Social Care Trust, Belfast, UK
27. Emma Lammey, Ulster Hospital, South Eastern Health and Social Care Trust, Belfast, UK
28. Mazen Matar, University Hospitals Birmingham NHS Trust, Birmingham, UK
29. Gordon Mazibrada, University Hospitals Birmingham NHS Trust, Birmingham, UK
30. James McDonald, Department of Clinical Neurosciences, Royal Infirmary of Edinburgh, Edinburgh, UK
31. Gavin McDonnell, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, UK
32. Ahmed Mubarak Mohamed, Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
33. David Paling, Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
34. Kate Petheram, South Tyneside and Sunderland NHS Foundation Trust, UK

35. David Rog, Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK
36. Klaus Schmierer, The Blizard Institute, Centre for Neuroscience, Surgery & Trauma, Queen Mary University of London, Barts and The London School of Medicine & Dentistry, London, UK
37. Emma Spector, South Tyneside and Sunderland NHS Foundation Trust, UK
38. Cord Spilker, Bradford Teaching Hospitals NHS Trust, UK
39. Anaïs Thouin, Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne, UK
40. Julie Webster, Mid and South Essex NHS Foundation Trust, Essex, UK,
41. Mark Willis, University Hospital of Wales, Cardiff, UK
42. Ray Wynford-Thomas, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, University Hospital of Wales, Cardiff, UK
43. Tadas Zuromskis, Department of Neurology, Great Western Hospitals NHS Foundation Trust

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The contemporary role of MRI in the monitoring and management of people with multiple sclerosis in the UK

ABSTRACT

Background - Compare the contemporary use of magnetic resonance imaging (MRI) in the monitoring and management of people with MS in the UK to current consensus guidelines.

Methods - This retrospective multicentre audit of clinical practice gathered data on 2567 patients with MS from 25 MS centres across the UK.

Results - Routine monitoring (44.7%), and recent clinical relapse (20.3%) were the most common scan indications. In routine monitoring, the addition of spinal imaging to brain showed no significant difference in disease modifying treatment (DMT) decision at subsequent clinical review. Approximately 1 in 5 gadolinium administered scans showed enhancement, and in 1 in 20 patients, gadolinium enhancement was the only evidence of radiological disease activity. Mean inter-scan intervals in relapsing-remitting MS for routine monitoring was 19.2 months (SD 20.7) with wide variation between centres. Only 53.8% of patients under progressive multifocal leukoencephalopathy (PML) surveillance met the recommended scanning frequency. MRI protocols demonstrated heterogeneity in the sequences used for diagnostic, monitoring and PML surveillance scans.

Conclusions – MS centres across the UK demonstrate varied practice and protocols when using MRI to monitor people with MS. In this cohort, gadolinium use and spinal imaging demonstrates limited impact on subsequent DMT decisions.

1. INTRODUCTION

Magnetic resonance imaging (MRI) of the brain and spine is routinely used in clinical practice to establish the diagnosis and disease burden of people with multiple sclerosis (MS). It is also used to guide eligibility for disease modifying treatments (DMTs), monitor response to these treatments, and plays a crucial role in pharmacovigilance for DMTs, especially natalizumab, where there is a risk of progressive multifocal leukoencephalopathy (PML). There are no widely implemented UK national consensus guidelines on the use of MRI in the management of people with MS, but efforts have begun to advance this process. (Saslow et al., 2020; Schmierer et al., 2019; Tomassini et al., 2020) The Magnetic Resonance Imaging in MS (MAGNIMS) study group published consensus recommendations on the use of MRI in the monitoring of people with MS in 2015, followed by guidelines on the MRI criteria to be used in the diagnostic process. (Filippi et al., 2016; Á. Rovira et al., 2015; Wattjes et al., 2015) In 2016 and then 2018, the consortium of MS centres produced revised technical guidelines on the MRI protocols for monitoring in MS, with an updated version currently in progress. (Consortium of MS centres, 2018; Saslow et al., 2020; Traboulsee et al., 2016) Most recently these organisations have worked together to produce new consensus recommendations on the use of MRI in patients with MS, taking account of the 2017 revisions in the McDonald diagnostic criteria. (Thompson et al., 2018; Wattjes et al., 2021). These consensus guidelines have provided a comprehensive set of MRI protocols, but their application can be challenging in diverse clinical settings. Variation in imaging practices across multiple centres has not previously been described.

The aim of this multicentre retrospective audit was to collect relevant clinical and imaging information from MS centres across the UK and compare them to published international consensus recommendations by the MAGNIMS study group and the consortium of MS centres. (Fernandes et al., 2021)

2. METHODS

MS centres around the UK in the National Health Service, were invited to participate in May 2020. A centre was eligible for participation if they provided clinical and radiological services for people with MS and had authorised access to clinical and radiological information on their patient sample. Data collection occurred between May and October 2020. Each centre sent data to Leeds Teaching Hospitals NHS Trust, which was also the co-ordinating centre and audit sponsor. Approval from the

Caldicott guardian was required in each participating centre prior to forwarding the anonymised audit data to the data controller.

i. Patient sample

Each centre reviewed medical records of 100 consecutive MS patients seen in specialist MS clinics run by MS specialist neurologists and MS specialist nurses from 1st September 2019. This date was chosen to give an adequate timeframe to collect data before the disruption to clinical services caused by the COVID-19 pandemic from March 2020. Each centre included patients attending a range of MS clinics e.g., DMT / Relapse / Transitioning / Rehabilitation / Continence. Inclusion criteria included an established diagnosis of MS or a probable diagnosis of MS in patients when the diagnostic criteria had not yet been met. Any patients that did not meet these inclusion criteria were excluded from the data collection.

ii. Audit dataset

Demographic data included birth year and sex, while disease-specific data included MS type, current DMT and year of diagnosis. As Expanded Disability Status Scale (EDSS) data may not be routinely collected at all sites or easily determined from patient records, disability information was simplified to ambulant without aid, with aid and non-ambulant. Dates of the most recent MRI scans, their indication, scan sequences, and any subsequent changes to DMT were gathered from patient records. Individual centres also provided the MRI sequences used in scanning MS patients for diagnostic, monitoring, relapse, and PML surveillance purposes. PML safety monitoring was deemed high or low risk based on the John Cunningham (JC) virus status of the patient (negative, low or high titre) and the duration of their treatment with natalizumab (less than or greater than 18 months). This approach is in line with the stratification used in expert recommendations published in 2016 and more recently by the physician management guidelines in 2020. (BIOGEN, 2020; McGuigan et al., 2016)

iii. Statistical analysis

Descriptive data are provided as case frequency and percentages. Independent sample t-tests were used for comparison of normally distributed, continuous outcome variables between patients. Chi-square tests were used for comparison of categorical data between patients with Bonferroni correction when multiple comparisons were made. Statistical significance was set at 0.05. Analysis was completed in IBM SPSS Statistics version 26 (IBM Corporation, Armonk, New York, USA).

3. RESULTS

i. Demographics

Twenty-five centres provided de-identified patient data and the MRI protocols used in their centres for brain and spinal cord imaging for people with MS. Five patients were excluded as they were missing most of the key data fields needed for analysis like scan indication, date, DMT outcome and scan findings (Figure 1).In total, 2,567 patients were included in the analysis, of which 1,814 (70.7%) were women. The median age was 48 years (IQR 39 - 57) and median time since diagnosis was 9 years (IQR 4 - 15).

Overall, 1,956 (76.2%) patients had relapsing-remitting MS (RRMS), 416 (16.2%) had secondary progressive MS (SPMS), and 191 (7.4%) patients had primary progressive MS (PPMS). One patient had radiologically isolated syndrome (RIS) and in three patients the MS disease course was not provided. Ambulation status was known for 2,519 patients, of whom 1,605 (63.7%) were ambulant without aid, 719 (28.5%) ambulant with aid, and 195 (7.7%) were non-ambulant. The number of patients on different DMTs is shown in Figure 2.

ii. Scanning indication and region imaged

Table 1 shows the indication for the most recent MRI scan, the region of the central nervous system imaged, and the number of scans, including post-gadolinium sequences in each case. Routine monitoring was the most common indication (44.7%), followed by recent clinical relapse (20.3%). Scans done for diagnostic evaluation, clinical relapse, and change of treatment purposes were more likely to include a brain and/or spinal protocol compared to other indications listed in Table 1 (66.7% vs. 48.0%).

iii. New and enhancing lesions

The number of new lesions was quantified by the reporting radiologist in 1,899 (89.7%) scans when a comparison scan was available. 987 (38.4%) out of 2,567 audited scans also included post gadolinium sequences. Gadolinium was used most commonly in patients with recent clinical relapse (59.6%) and treatment change (51.0%). Table 2 shows the frequency of patients that reported new or enhancing lesions based on scan indication. Of the 166 patients with gadolinium enhancing lesions, 122 of these (73.5%) were concurrently noted to have new T2 lesions, while in the remaining 44 patients (5.3% of all gadolinium-enhanced scans), lesion enhancement was the only evidence of new

radiological disease activity. In those patients undergoing imaging for routine monitoring with i reported presence or absence of new T2 and enhancing lesions (n=336), 61 (17.6%) had enhancing lesions, and in 29 (8.6%) patients the enhancement was the only evidence of radiological disease activity. Similar results were seen when scans were performed due to clinical relapse (n=249), where 68 (27.3%) patients had enhancing lesions, and in 7 (2.8%) patients the enhancement was the only evidence of radiological disease activity.

iv. Clinical outcomes following MRI

We analysed DMT sequencing at subsequent clinical review (following the most recent MRI scan) in 2,417 patients. 411 patients (17.0%) had a change in their DMT while 1,908 (78.9%) had no change in treatment. 101 patients (3.9%) had not been reviewed in clinic following their MRI scan at the time of the audit. The presence of new lesions on MRI was significantly associated with a change in DMT at the next clinic review (48.2% vs. 7.2%, $p<0.001$).

Among the 1,147 patients with scans performed for routine monitoring, 1,090 patients (95.0%) had data available on subsequent DMT decisions., 87 (8.0%) had a subsequent DMT change, suggesting that 12.5 routine monitoring scans were performed for one patient's treatment to be altered. 556 patients had imaging of the brain only for routine monitoring and 571 had imaging of the brain and spine. There was no difference in the rate of subsequent DMT changes between these groups (8.2% vs. 7.9%, $p=0.954$). The presence of new T2 lesions in patients with RRMS during routine monitoring was associated with DMT change at next clinic visit in 37.7% vs. 3.1% in those without new lesions ($p<0.001$). In the same group, the presence of one or more gadolinium enhancing lesions was associated with a change in DMT at next clinic visit in 21.6% of patients vs. 7.7% in those without enhancement ($p=0.01$).

v. PML surveillance

Table 3 shows the breakdown of the 229 patients on natalizumab with information on scan interval, treatment duration and JC virus serostatus. 13 of 31 (41.9%) high risk PML patients (high JC virus titre, treatment duration > 18months), failed to meet recommended PML scan monitoring intervals of less than 6 months. (BIOGEN, 2020) Similarly, 90 of 192 (46.9%) low-risk patients (low JCV virus titre or negative and treatment duration < 18months), failed to meet recommended MRI scanning intervals of less than 12 months.

vi. Scanning frequency

People with RRMS were scanned significantly more frequently compared to people with progressive MS, at a mean inter-scan interval of 19.2 months (SD 20.7) vs. 31.3 months (SD 31.4) respectively ($p<0.001$). People with PPMS were scanned significantly more frequently than people with SPMS, at a mean inter-scan interval of 26.0 months (SD 24.6) vs. 36.1 months (SD 39.8) respectively ($p=0.001$)

Patients on high efficacy treatments, i.e., autologous haematopoietic stem cell transplantation, alemtuzumab, cladribine, natalizumab and ocrelizumab, had a significantly shorter interval between scans, with a mean of 13.6 months (SD 11.6), compared to 21.1 months (SD 23.0) for patients on lower efficacy treatments (all remaining DMTs), ($p<0.001$) (Figure 3) Figure 4 shows the scanning frequency in months between centres for routine monitoring of ambulant RRMS patients.

vii. MRI protocols

The scan sequences used by each centre were compared to the protocols suggested by MAGNIMS and the consortium of MS centres. (Consortium of MS centres, 2018; À. Rovira et al., 2015) The full list of sequences used in diagnostic, monitoring and PML surveillance protocols are shown in Supplementary Tables 1 - 3. Information on the field strength of scanners was not collected.

For routine monitoring scans, T2-weighted and FLAIR remain the most common sequences, with DWI included to assess for active disease and during PML surveillance. In 23/25 centres, gadolinium contrast was administered only if the requesting clinician specified post-contrast imaging to look for disease activity, or to assess for radiological evidence of relapse activity. 41.1% of all scans had gadolinium administered, suggesting that clinicians continue to request gadolinium commonly on a case-by-case basis.

Spinal imaging in addition to brain imaging for routine monitoring is not contained in the protocol for any participating centre. However, the spine was included for 51.1% of all routine monitoring scans as shown in Table 1, demonstrating significant variation in clinical practice. 15/25 centres routinely obtain 3D/volumetric sequences for diagnostic and monitoring scans, suggesting a lack of agreement on the clinical utility, or availability of these sequences.

4. DISCUSSION

This multicentre audit captures significant variation in clinical practice when imaging people with MS amongst centres in the UK, in comparison to the MAGNIMS and consortium of MS centres recommendations that were produced in 2015 and 2016 respectively. Table 4 outlines a number of areas where UK clinical practice does not meet these recommended guidelines.

i. The use of spinal imaging and gadolinium enhanced sequences

The inclusion of spinal sequences in diagnostic MRI scans for patients with clinically isolated syndrome has demonstrated benefits in meeting MS diagnostic criteria for dissemination in space. Asymptomatic spinal cord lesions in combination with asymptomatic brain lesions, contribute significantly to predicting future disease course. (Brownlee et al., 2019; Zecca et al., 2016) However, guidelines do not recommend routine monitoring with spinal cord imaging unless there are new symptoms applicable to the spinal cord or if spinal cord activity will impact on subsequent DMT treatment decisions. (Consortium of MS centres, 2018; Wattjes et al., 2021) While only one centre included spinal imaging as a routine part of their MRI protocol for patients with MS, a surprising finding of this audit was that over half of scans performed for routine monitoring included spinal sequences. In ambulant patients with RRMS, the addition of spinal imaging to routine brain imaging did not increase the rate of subsequent DMT change at the next clinic review, suggesting a limited contribution to clinical decision making. (Bot et al., 2004; Okuda et al., 2011; Thompson et al., 2018) This finding supports current consensus guidelines, and suggests that in current UK practice, the efficiency of the regular use of routine spinal cord imaging in the monitoring of patients with MS should be reviewed. Previous studies indicated a strong association between brain and spinal cord inflammatory activity, although the ability to detect these changes rely on the field strength of the scanner and use of specific sequences, like Short Tau Inversion Recovery (STIR). (Silver et al., 2001; Thorpe et al., 1996)

Demonstration of gadolinium enhancement remains an important tool for identifying new inflammatory activity, and hence has particular importance on initial imaging to demonstrate dissemination in time, or in situations where no previous imaging is available. However, with serial MRI monitoring of persons with MS, active disease can be identified by new/enlarging T2 lesions, hence guidelines do not recommend routine use of gadolinium in follow-up imaging unless it is required due to particular clinical circumstances, such as confirmation of disease activity, without a recent scan for comparison

or when specified by DMT starting criteria (Wattjes et al., 2021) . Concerns also remain over the potential accumulation of gadolinium within body tissues. (Fraum et al., 2017)

Eighteen centres in our audit specified that they only administer gadolinium if specifically requested by the clinician, though 33.5% of routine monitoring scans included post-gadolinium sequences. (Guo et al., 2018) While 18.6% of scans performed with gadolinium demonstrated enhancing lesions, such enhancement was the only evidence of disease activity in only 5.3% of patients. However, the quantification of enlarging T2 lesions or presence of diffusion restriction wasn't included as other methods of measuring disease activity. Gadolinium was used most frequently in imaging performed post clinical relapse (59.6% of patients) and this indication had the highest rates of enhancing lesions (27.3%). However, due to the higher frequency of new T2 lesions, the additional yield on identifying radiological activity was lower than for other indications, with just 2.8% of relapse patients having gadolinium enhancement as the only feature of radiological disease activity.

While administration of gadolinium marginally increases the identification of radiological activity, enhancement of new lesions is temporary and in clinical practice the time interval of the scan after relapse is important in order to identify the symptomatic lesion. (Cotton et al., 2003; Miller et al., 1993) Although new hyperintense T2 lesions are more difficult to identify on visual inspection compared to gadolinium enhancement, and more so for identifying changes in enlarging lesions, a number of studies have shown a strong correlation between T2 lesions, brain atrophy and disease progression. (Río et al., 2009; Rudick et al., 2006; Stevenson et al., 2004; Tomassini et al., 2020) Serial follow-up assessment with double inversion recovery or FLAIR sequences alone allow the identification of most hyperintense lesions which enhance, and more advanced techniques like diffusion tensor imaging based fractional anisotropy have shown the ability to differentiate between enhancing and non-enhancing lesions. (Gupta et al., 2017; Sadigh et al., 2019) Automated subtraction techniques may also soon play a more prominent role in the long-term monitoring of patients on DMT. (Moraal et al., 2009) Overall, our results suggest that regular administration of gadolinium results in a small increase in the identification of radiological activity and given the concerns over the long-term safety of such agents, the use of gadolinium could be more conservative.

ii. Variations in MRI scanning frequency between centres

We demonstrate significant heterogeneity in scanning intervals between MRI scans amongst centres and MS subtypes. As anticipated, scanning intervals in progressive MS patients were significantly longer than in the RRMS group, but 52.4% (318/607 scans) of scans in progressive patients were done for routine monitoring, recent clinical relapse or deterioration in their condition, despite the lack of DMTs for this patient group. This audit was completed prior to the introduction of a licensed DMT for SPMS in the UK, but after the licensing of ocrelizumab for certain PPMS patients. (NICE, 2020, 2019) Given the recent approval for Siponimod in SPMS in the UK, the clinical utility of scanning people with progressive MS, especially for routine monitoring, will be likely to change in the near future. Our data suggest that the increase in MRI resources required to support demonstration of Siponimod eligibility will represent a significant additional cost and use of NHS MRI resources.

Figure 4, highlights the variation seen amongst centres in this audit with regards to routine MRI scanning intervals in ambulant patients with RRMS. This relatively clinically homogenous group should have scanning intervals for routine monitoring of RRMS patients on DMTs between 12 and 36 months, based on international recommendations in 2015, but the most recent version of these guidelines have taken a more nuanced approach specifying yearly scans during the initial phase of treatment, which can then be relaxed in clinically stable patients with no radiological disease activity. (Wattjes et al., 2021, 2015) Our data shows that the 12 scans done on average to change one patient's treatment (8.3% rate of DMT change after a scan) is higher than the 4.4% rate of change in DMTs after scans seen in other MRI monitoring studies. (Cohan et al., 2016) While our dataset only included 100 patients from each MS centre, this data was collected systematically and demonstrated significant differences between centres that is likely to reflect true local variations in clinical practice (one-way ANOVA $p<0.001$). The variation seen in these scan intervals is likely due to clinical practice and local provision of MRI scanners, and highlights the real world difficulties in pursuing treatment goals like "no evidence of disease activity" which rely on regular MRI monitoring. (Giovannoni et al., 2015; Guevara et al., 2019) This variation is also seen in the PML surveillance scanning intervals which have better defined criteria for scanning frequency based on JCV risk status. (BIOGEN, 2020; McGuigan et al., 2016) Despite a limited scanning protocol consisting of FLAIR, T2-weighted and diffusion-weighted imaging in PML surveillance patients, the frequency of scans adds significant burden to local radiology services. This is reflected in our findings, as almost all centres did not meet

the scanning interval limits set by the guidelines for all their high and low risk PML surveillance patients.

5. LIMITATIONS

A limitation of the study was restricting the scanning indication of the most recent MRI scan to just a single indication. This approach overlooks secondary indications for MRI scanning in these patients, such as “re-baselining” after a switch of DMT. Scans with a “re-baselining” indication may have also been referred to as “routine monitoring”, thus seemingly resulting in an underestimate of scans done for re-baseline indications as seen in Table 1. Sampling bias was limited by collecting consecutive patients from each centre. However, we recognise that clinic patient lists may have been organised differently between centres. Whilst inclusion of progressive MS patients provided a heterogenous group, it allowed for a more comprehensive overview of scanning practices in MS centres. MS centres provide services to differing numbers of pwMS, and smaller centres might be more heavily weighted in the analyses as we collected 100 patients rather than a proportion of patients from each centre. However, we believe that we have collected a comparable sample of patients, from several centres to be able to describe current national practices with some accuracy. DMT initiation dates were not collected, and data on subsequent DMT changes only considered the next clinical appointment following the MRI scans, hence may have missed a decision to change DMT that occurred at a later date. Imaging information like area imaged, and number of lesions was only collected on the most recent scan for each patient, limiting any analysis of the significance of the number of lesions or presence of enhancement on clinical progression. Reporting expertise is an important factor as well, information on which we did not collect in this audit, with neuroradiologists having a higher detection rate of new CNS lesions compared to non-neuroradiologists.(Wang et al., 2017)

6. CONCLUSIONS

We have captured a large, representative sample of patients to demonstrate the contemporary use of MRI for MS patients around the UK. Scanning practices frequently diverged from consensus guidelines and we have identified the regular use of contrast enhancement and spinal imaging as areas that require further investigation to clarify their efficiency. More uniform adherence to international consensus recommendations may reduce variations in scanning frequency and improve efficiency, which will be particularly important as demands increase due to the availability of DMTs for

progressive MS. Semi-automated tools to facilitate assessment of MRI in routine follow-up also deserve further implementation research. Evidence suggests that using such tools to guide radiologists may reduce both interobserver variability and reporting time. (Dahan et al., 2018) While data have yet to be produced to confirm the utility of these measures in clinical practice there is a need to consider these and other emerging analytical technologies for clinical decision support when formulating protocols to be used across the UK. (Schmierer et al., 2019)

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Data availability - The dataset is available to all authors and may be provided on request from suitably qualified researchers to the corresponding author, subject to a data access agreement.

REFERENCES

BIOGEN, 2020. Physician Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI Therapy (Version 18).

Bot, J.C.J., Barkhof, F., Polman, C.H., Lycklama À Nijeholt, G.J., De Groot, V., Bergers, E., Ader, H.J., Castelijns, J.A., 2004. Spinal cord abnormalities in recently diagnosed MS patients: Added value of spinal MRI examination. Neurology 62, 226–233. https://doi.org/10.1212/WNL.62.2.226

Brownlee, W.J., Altmann, D.R., Prados, F., Miszkiel, K.A., Eshaghi, A., Gandini Wheeler-Kingshott, C.A.M., Barkhof, F., Ciccarelli, O., 2019. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. Brain 142, 2276–2287. https://doi.org/10.1093/brain/awz156

Cohan, S., Chen, C., Baraban, E., Stuchiner, T., Grote, L., 2016. MRI utility in the detection of disease activity in clinically stable patients with multiple sclerosis: A retrospective analysis of a community based cohort. BMC Neurol. 16, 184. https://doi.org/10.1186/s12883-016-0699-8

Consortium of MS centres, 2018. Revised Guidelines of the Consortium of MS Centers MRI Protocol for the Diagnosis and Follow-up of MS.

Cotton, F., Weiner, H.L., Jolesz, F.A., Guttmann, C.R.G., 2003. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. Neurology 60, 640–646. https://doi.org/10.1212/01.WNL.0000046587.83503.1E

Dahan, A., Wang, W., Gaillard, F., 2018. Computer-Aided Detection Can Bridge the Skill Gap in Multiple Sclerosis Monitoring. J. Am. Coll. Radiol. 15, 93–96. https://doi.org/10.1016/j.jacr.2017.06.030

Fernandes, L., Allen, C.M., Williams, T., Tallantyre, E., Evangelou, N., Chataway, J., Ford, H., 2021. A multicentre audit on the use of MRI in the monitoring and management of people with Multiple Sclerosis [WWW Document]. URL https://www.institutemh.org.uk/research/nottingham-ms-research-group/publications (accessed 7.14.21).

Filippi, M., Rocca, M.A., Ciccarelli, O., De Stefano, N., Evangelou, N., Kappos, L., Rovira, A., Sastre-Garriga, J., Tintorè, M., Frederiksen, J.L., Gasperini, C., Palace, J., Reich, D.S., Banwell, B., Montalban, X., Barkhof, F., 2016. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 15, 292–303. https://doi.org/10.1016/S1474-4422(15)00393-2

Fraum, T.J., Ludwig, D.R., Bashir, M.R., Fowler, K.J., 2017. Gadolinium-based contrast agents: A comprehensive risk assessment. J. Magn. Reson. Imaging 46, 338–353. https://doi.org/10.1002/jmri.25625

Giovannoni, G., Turner, B., Gnanapavan, S., Offiah, C., Schmierer, K., Marta, M., 2015. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult. Scler. Relat. Disord.

https://doi.org/10.1016/j.msard.2015.04.006

Guevara, C., Garrido, C., Martinez, M., Farias, G.A., Orellana, P., Soruco, W., Alarcón, P., Diaz, V., Silva, C., Kempton, M.J., Barker, G., de Grazia, J., 2019. Prospective Assessment of No Evidence of Disease Activity-4 Status in Early Disease Stages of Multiple Sclerosis in Routine Clinical Practice. Front. Neurol. 10, 788. https://doi.org/10.3389/fneur.2019.00788

Guo, B.J., Yang, Z.L., Zhang, L.J., 2018. Gadolinium Deposition in Brain: Current Scientific Evidence and Future Perspectives. Front. Mol. Neurosci. 11, 335. https://doi.org/10.3389/fnmol.2018.00335

Gupta, A., Al-Dasuqi, K., Xia, F., Askin, G., Zhao, Y., Delgado, D., Wang, Y., 2017. The use of noncontrast quantitative MRI to detect gadolinium-enhancing multiple sclerosis brain lesions: A systematic review and meta-analysis. Am. J. Neuroradiol. 38, 1317–1322. https://doi.org/10.3174/ajnr.A5209

McGuigan, C., Craner, M., Guadagno, J., Kapoor, R., Mazibrada, G., Molyneux, P., Nicholas, R., Palace, J., Pearson, O.R., Rog, D., Young, C.A., 2016. Stratification and monitoring of natalizumabassociated progressive multifocal leukoencephalopathy risk: Recommendations from an expert group. J. Neurol. Neurosurg. Psychiatry 87, 117–125. https://doi.org/10.1136/jnnp-2015-311100

Miller, D.H., Barkhof, F., Nauta, J.J.P., 1993. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. Brain 116, 1077–1094. https://doi.org/10.1093/brain/116.5.1077

Moraal, B., van den Elskamp, I.J., Knol, D.L., Uitdehaag, B.M.J., Geurts, J.J.G., Vrenken, H., Pouwels, P.J.W., van Schijndel, R.A., Meier, D.S., Guttmann, C.R.G., Barkhof, F., 2009. Long-interval T2w subtraction MRI: A powerful new outcome measure in MS trials. Ann. Neurol. 67, 667–675. https://doi.org/10.1002/ana.21958

NICE, 2020. Final appraisal document: 1 | Siponimod for treating secondary progressive multiple sclerosis | Guidance. NICE.

NICE, 2019. Overview | Ocrelizumab for treating primary progressive multiple sclerosis | Guidance. NICE.

Okuda, D.T., Mowry, E.M., Cree, B.A.C., Crabtree, E.C., Goodin, D.S., Waubant, E., Pelletier, D., 2011. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology 76, 686–692. https://doi.org/10.1212/WNL.0b013e31820d8b1d

Río, J., Castilló, J., Rovira, A., Tintoré, M., Sastre-Garriga, J., Horga, A., Nos, C., Comabella, M., Aymerich, X., Montalbán, X., 2009. Measures in the first year of therapy predict the response to interferon β in MS. Mult. Scler. 15, 848–853. https://doi.org/10.1177/1352458509104591

Rovira, À., Wattjes, M.P., Tintoré, M., Tur, C., Yousry, T. a., Sormani, M.P., De Stefano, N., Filippi,

M., Auger, C., Rocca, M. a., Barkhof, F., Fazekas, F., Kappos, L., Polman, C., Miller, D., Montalban, X., 2015. MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients. Nat. Rev. Neurol. 11, 1–12. https://doi.org/10.1038/nrneurol.2015.106

Rovira, Á., Wattjes, M.P., Tintoré, M., Tur, C., Yousry, T.A., Sormani, M.P., De Stefano, N., Filippi, M., Auger, C., Rocca, M.A., Barkhof, F., Fazekas, F., Kappos, L., Polman, C., Miller, D., Montalban, X., 2015. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis - Clinical implementation in the diagnostic process. Nat. Rev. Neurol. 11, 471–482. https://doi.org/10.1038/nrneurol.2015.106

Rudick, R.A., Lee, J.-C., Simon, J., Fisher, E., 2006. Significance of T2 lesions in multiple sclerosis: A 13-year longitudinal study. Ann. Neurol. 60, 236–242. https://doi.org/10.1002/ana.20883

Sadigh, G., Saindane, A.M., Waldman, A.D., Lava, N.S., Hu, R., 2019. Comparison of unenhanced and gadolinium-enhanced imaging in multiple sclerosis: Is contrast needed for routine follow-up MRI?, in: American Journal of Neuroradiology. American Society of Neuroradiology, pp. 1476–1480. https://doi.org/10.3174/ajnr.A6179

Saslow, L., Li, D.K.B., Halper, J., Banwell, B., Barkhof, F., Barlow, L., Costello, K., Damiri, P., Dunn, J., Giri, S., Maes, M., Morrow, S.A., Newsome, S.D., Oh, J., Paul, F., Quarterman, P., Reich, D.S., Shewchuk, J.R., Shinohara, R.T., Hecke, W. Van, van de Ven, K., Wallin, M.T., Wolinsky, J.S., Traboulsee, A., 2020. An International Standardized Magnetic Resonance Imaging Protocol for Diagnosis and Follow-up of Patients with Multiple Sclerosis. Int. J. MS Care 22, 226–232. https://doi.org/10.7224/1537-2073.2020-094

Schmierer, K., Campion, T., Sinclair, A., Van Hecke, W., Matthews, P.M., Wattjes, M.P., 2019. Commentary: Towards a standard MRI protocol for multiple sclerosis across the UK. Br. J. Radiol. https://doi.org/10.1259/bjr.20180926

Silver, N.C., Good, C.D., Sormani, M.P., MacManus, D.G., Thompson, A.J., Filippi, M., Miller, D.H., 2001. A modified protocol to improve the detection of enhancing brain and spinal cord lesions in multiple sclerosis. J. Neurol. 248, 215–224. https://doi.org/10.1007/s004150170229

Stevenson, V.L., Ingle, G.T., Miller, D.H., Thompson, A.J., 2004. Magnetic resonance imaging predictors of disability in primary progressive multiple sclerosis: A 5-year study. Mult. Scler. 10, 398–401. https://doi.org/10.1191/1352458504ms1055oa

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. https://doi.org/10.1016/S1474-4422(17)30470-2

Thorpe, J.W., Kidd, D., Moseley, I.F., Kendall, B.E., Thompson, A.J., MacManus, D.G., McDonald, W.I., Miller, D.H., 1996. Serial gadolinium-enhanced MRI of the brain and spinal cord in early relapsing-remitting multiple sclerosis. Neurology 46, 373–378. https://doi.org/10.1212/WNL.46.2.373

Tomassini, V., Sinclair, A., Sawlani, V., Overell, J., Pearson, O.R., Hall, J., Guadagno, J., 2020. Diagnosis and management of multiple sclerosis: MRI in clinical practice. J. Neurol. 267, 2917–2925. https://doi.org/10.1007/s00415-020-09930-0

Traboulsee, A., Simon, J.H., Stone, L., Fisher, E., Jones, D.E., Malhotra, A., Newsome, S.D., Oh, J., Reich, D.S., Richert, N., Rammohan, K., Khan, O., Radue, E.W., Ford, C., Halper, J., Li, D., 2016. Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. Am. J. Neuroradiol. https://doi.org/10.3174/ajnr.A4539

Wang, W., Van Heerden, J., Tacey, M.A., Gaillard, F., 2017. Neuroradiologists compared with non-neuroradiologists in the detection of new multiple sclerosis plaques. Am. J. Neuroradiol. 38, 1323–1327. https://doi.org/10.3174/ajnr.A5185

Wattjes, M.P., Ciccarelli, O., Reich, D.S., Banwell, B., de Stefano, N., Enzinger, C., Fazekas, F., Filippi, M., Frederiksen, J., Gasperini, C., Hacohen, Y., Kappos, L., Li, D.K.B., Mankad, K., Montalban, X., Newsome, S.D., Oh, J., Palace, J., Rocca, Maria A, Sastre-Garriga, J., Tintoré, M., Traboulsee, A., Vrenken, H., Yousry, T., Barkhof, F., Rovira, À., Wattjes, M.P., Ciccarelli, O., de Stefano, N., Enzinger, C., Fazekas, F., Filippi, M., Frederiksen, J., Gasperini, C., Hacohen, Y., Kappos, L., Mankad, K., Montalban, X., Palace, J., Rocca, María A, Sastre-Garriga, J., Tintore, M., Vrenken, H., Yousry, T., Barkhof, F., Rovira, A., Li, D.K.B., Traboulsee, A., Newsome, S.D., Banwell, B., Oh, J., Reich, D.S., Reich, D.S., Oh, J., 2021. 2021 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. https://doi.org/10.1016/s1474-4422(21)00095-8

Wattjes, M.P., Rovira, À., Miller, D., Yousry, T.A., Sormani, M.P., De Stefano, N., Tintoré, M., Auger, C., Tur, C., Filippi, M., Rocca, M.A., Fazekas, F., Kappos, L., Polman, C., Barkhof, F., Montalban, X., 2015. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis - Establishing disease prognosis and monitoring patients. Nat. Rev. Neurol. 11, 597–606. https://doi.org/10.1038/nrneurol.2015.157

Zecca, C., Disanto, G., Sormani, M.P., Riccitelli, G.C., Cianfoni, A., Del Grande, F., Pravatà, E., Gobbi, C., 2016. Relevance of asymptomatic spinal MRI lesions in patients with multiple sclerosis. Mult. Scler. 22, 782–791. https://doi.org/10.1177/1352458515599246

TABLES

Indication for most recent MRI scan	Region imaged frequency of cases				Percentage of scans with gadolinium administered† (%)	Total cases for each indication (%)
	Brain only	Brain and spine	Spine only	Unclear		
Routine monitoring	556	571	15	5	33.5	1147 (44.7)
Recent clinical relapse	115	325	37	44	59.6	521 (20.3)
Treatment initiation / switch	80	113	5	4	51.0	202 (7.9)
Diagnostic (to demonstrate DIT)	67	112	12	8	44.8	199 (7.8)
PML Safety monitoring - Low risk	102	56	0	1	32.7	159 (6.2)
PML Safety monitoring - High risk	48	14	0	3	42.2	65 (2.5)
Rebaseline*	24	4	2	1	9.7	31 (1.2)
Deterioration of condition	8	19	1	1	27.6	29 (1.1)

Table 1. Most recent scan by indication, area imaged and use of gadolinium. Cases were constrained to select one indication per scan. 187 scans did not specify the region imaged or the indication for the scan and are not represented in the table. 34 scans were done for a non-MS related indication and are also not represented in the table. 24 scans were imported and no indication for the scan was available. *Rebaseline scans were done after treatment was initiated compared to Treatment initiation/switch which was done prior to treatment change. †Based on scans with information on whether gadolinium was used. *PML, Progressive multifocal leukoencephalopathy, DIT, Dissemination in time*

Indication for most recent MRI scan	Number of cases with new T2 weighted lesions				Number of cases with gadolinium enhancing lesions			
Number of lesions	**None**	**1**	**≥2**	**New, not quantified**	**None**	**1**	**≥2**	**Present, not quantified**
Routine monitoring	870	76	44	56	305	17	13	31
Recent clinical relapse	248	64	53	88	209	40	20	17
Treatment initiation / switch	107	19	25	34	72	7	8	7
Diagnostic (to demonstrate DIT)	51	13	18	24	55	8	5	9
PML Safety monitoring	204	4	3	4	78	1	0	0
Rebaseline	20	3	5	2	3	0	0	0
Deterioration of condition	15	0	0	3	6	0	0	0

Table 2. Disease activity detected in most recent scan based on scan indication

JC virus serostatus	Natalizumab treatment duration	Number of cases	Average scan interval / months (S.D.)	Percentage not meeting criteria
High titre	<18 months	7	5.8 (2.8)	41.9%
	≥18 months	31	5.9 (3.3)	
Low titre	<18 months	18	12.0 (8.7)	46.9%
	≥18 months	31	7.8 (3.3)	
Negative	<18 months	28	12.1 (10.7)	
	≥18 months	114	12.1 (3.6)	

Table 3. Scan intervals of cases at risk of PML based on Natalizumab treatment duration and JC virus serostatus

Guideline Recommendation	Current Practice as audited
Ambulant people with RRMS should have MRI monitoring every 12 - 36 months	8% of patients on DMT failed to meet this criteria; 20% of patients not on DMT failed to meet this criteria
Spinal imaging during follow-up should be performed only if there are new symptoms applicable to the spinal cord	50% of routine monitoring imaging included spinal cord sequences in additional to brain
High risk and low risk PML should have MRI monitoring every 6 and 12 months respectively	46% of patients requiring PML surveillance did not meet these scan frequency criteria
The acquisition of gadolinium enhanced sequences should be limited in routine monitoring	34% of scans done for routine monitoring purposes included post-contrast sequences

Table 4. Comparison of UK practice to published guidelines from MAGNIMS (2015) and the Consortium of MS centres on the use of MRI (2016) in multiple sclerosis

FIGURES

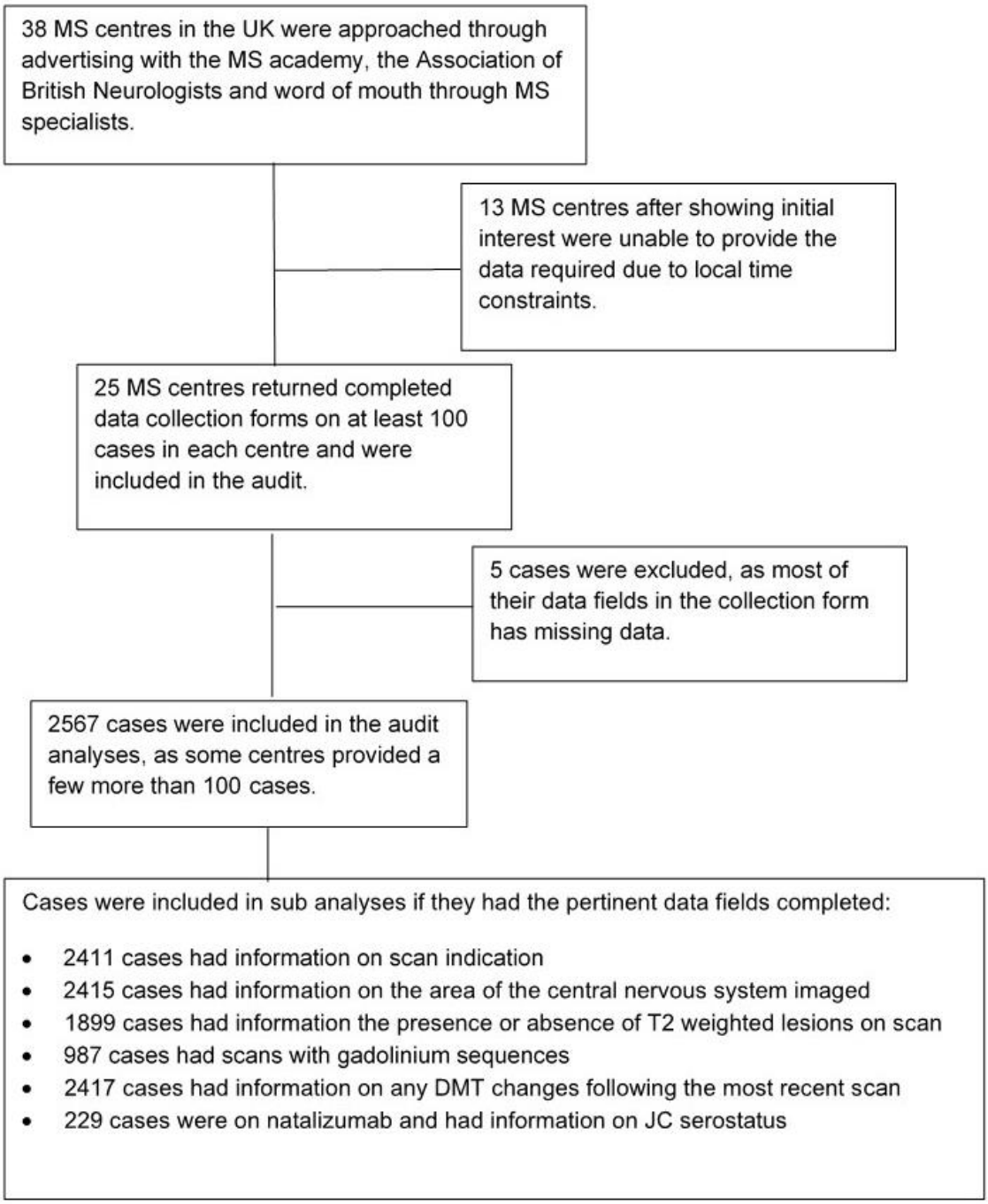

Figure 1. Flowchart illustrating centre and case selection for inclusion in the study.

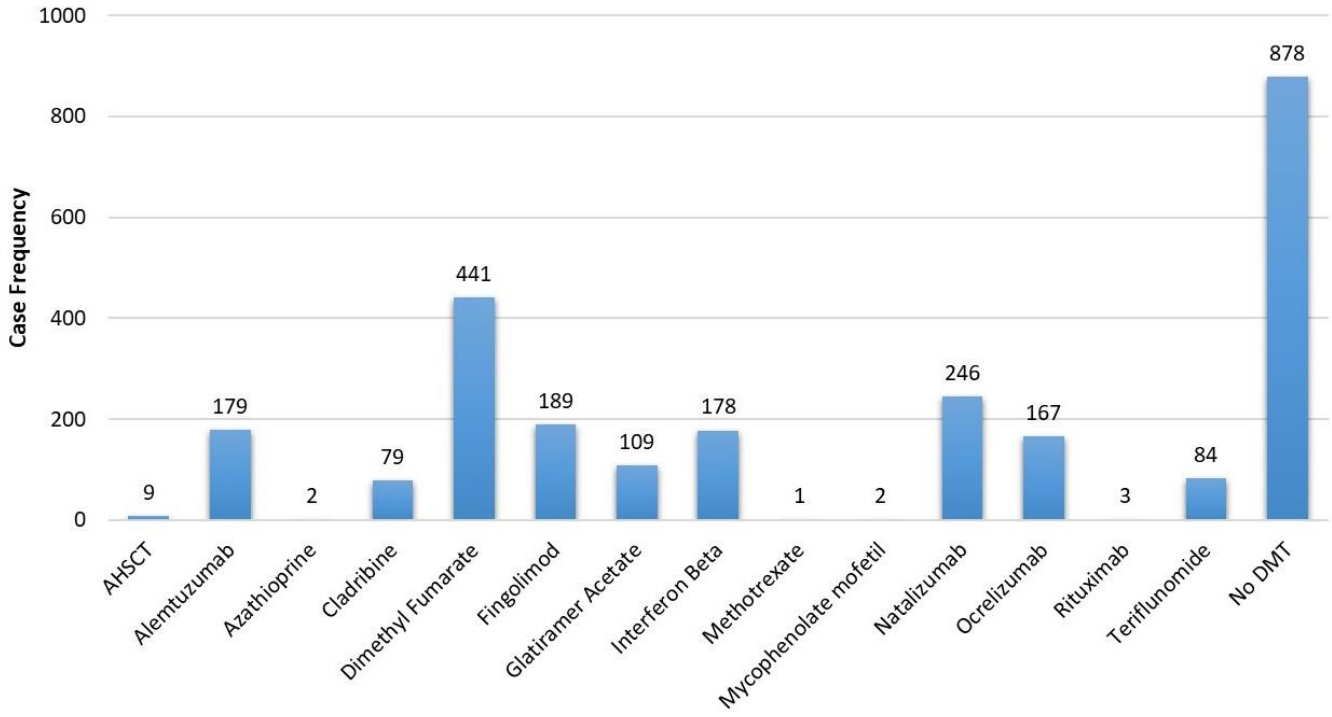

Figure 2. Number of cases on different disease modifying treatments.

Of the 878 patients not on any DMT, 377 had RRMS (19.3% of people with RRMS), 166 had PPMS (86.9% of people with PPMS), 331 had SPMS (79.6% of people with SPMS), 3 had no diagnosis, and 1 had RIS. AHSCT, autologous haematopoietic stem cell transplantation

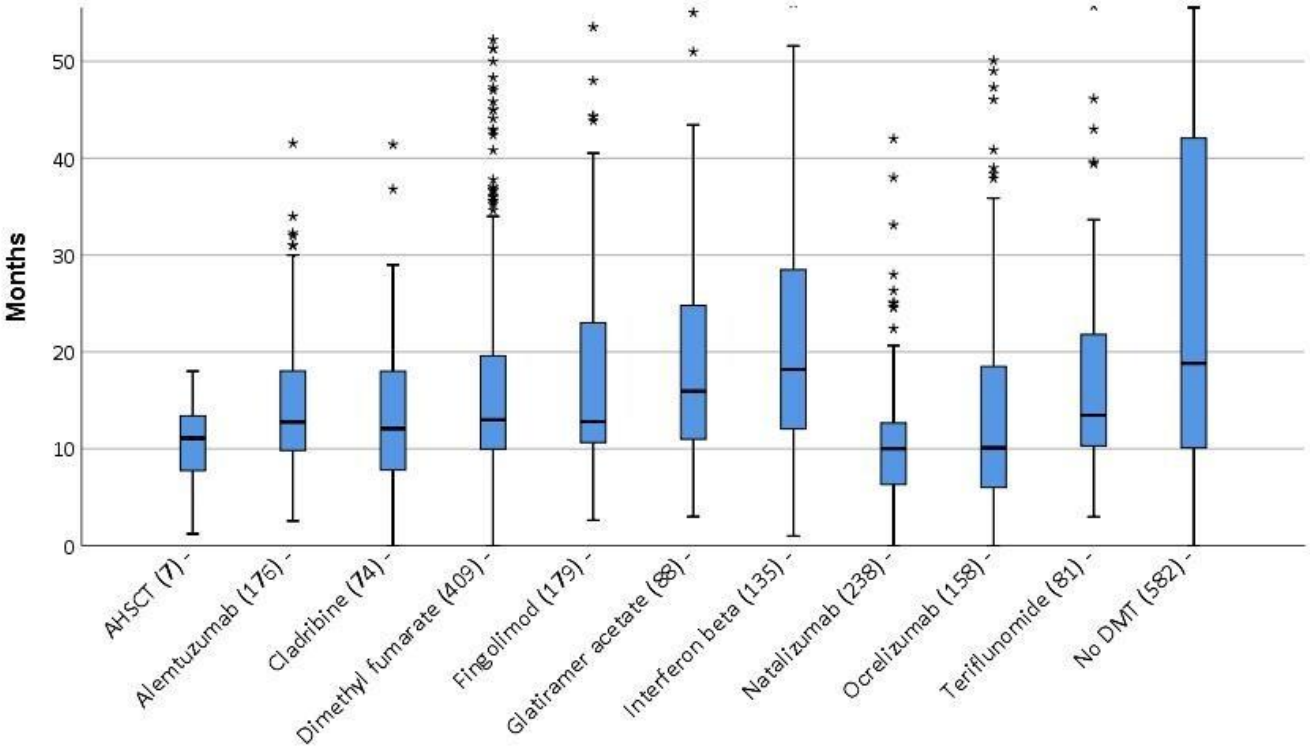

Figure 3. Boxplots showing median and interquartile ranges of the intervals between scans for MS patients based on their DMT. A limited y-axis scale is selected to represent the range of scan intervals on the graph. Several outliers have not been shown on the higher end of the scale. Number of cases on each DMT is shown in brackets, only cases with two or more MRI scans are included. Patients on azathioprine (2), methotrexate (1), mycophenolate mofetil (2) and rituximab (2) were not included as they each had less than 5 cases. AHSCT, autologous haematopoietic stem cell transplantation

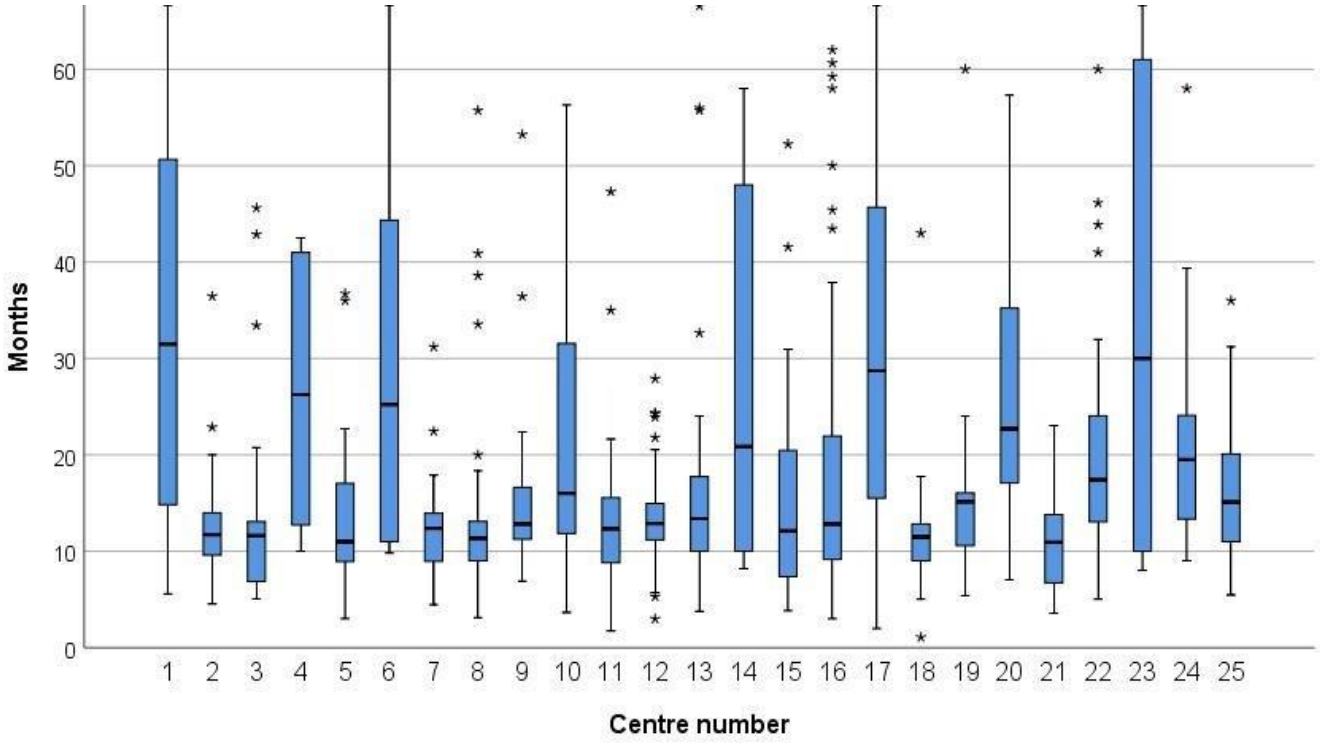

Figure 4. Boxplots showing median and interquartile ranges of the intervals between scans, by MS centre, for routine monitoring of ambulant RRMS patients. A limited y-axis scale is selected to represent the range of scan intervals on the graph. Outliers have not been shown on the higher end of the scale. Given this relatively clinically homogenous sample, the differences seen here are likely to represent variations in local scanning provision and practices.

SUPPLEMENTARY DATA

Supplementary Table 1. MRI sequences done in centres for diagnostic purposes in suspected MS cases

	Brain Sequences											Spine Sequences†				
	3D IR-prep GE T1	2D T2 FLAIR	3D/Vol T2 FLAIR	2D Axial/Sagittal T1	2D Axial T2	3D Axial T2	2D Axial DWI	Pre-Gad 2D/3D Axial T1	SWI	Post Gad 2D/3D Axial T1	Axial 2D PD	Sagittal / Axial T2	PD	STIR	T1-PSIR	Post Gad T1
Consortium	✓	✓	✓		✓	✓	✓			✓		✓	✓	✓	✓	✓
MAGNIMS		✓	✓		✓					✓	✓	✓	✓	✓		✓
1		✓			✓		✓	✓		✓		✓		✓		✓
2			✓		✓							✓	✓	✓		*
3		✓		✓	✓		✓									
4			✓	✓	✓		✓			*		✓				
5			✓		✓		✓	*		*		✓		✓		*
6	✓	✓	✓		✓		✓	*		*	✓	*		*		*
7		✓		✓	✓		✓			*						
8			✓	✓	✓			*		*		✓		✓		*
9	✓					✓		✓		✓						
10			✓	✓	✓		✓			*						
11			✓		✓		✓			*						
12		✓		✓	✓		✓	*		*		✓				
13		✓			✓		✓	✓		*		✓		✓		*
14			✓		✓		✓	*		*		✓				*
15		✓			✓			*		*		✓				*
16			✓		✓		✓			*						
17			✓	✓	✓		✓		✓							
18		✓			✓		✓	*		*		✓				*
19		✓		✓	✓		✓					✓				*
20			✓		✓		✓	*		*		✓		✓		*
21			✓	✓	✓		✓			*						
22	✓		✓				✓			*	✓			✓		*
23			✓	✓	✓		✓			*						
24	✓	✓		✓	✓		✓			*		✓				*
25		✓		✓	✓		✓	*		*	✓	✓		✓		*

*✓, scan sequences are included routinely; *****, scan sequences are only included when requested by the clinician; †, Spinal sequences are only included for centres which specifically included spinal scans in their diagnostic protocols, Centres 3,7,9,10,11,16,17,21 and 23 did not provide this information; 2D, two-dimensional; 3D, three-dimensional; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; Gad, gadolinium; GE, gradient echo; IR, inversion recovery; PD, proton density; PSIR, phase-sensitive inversion recovery; STIR, short tau inversion-recovery; SWI, susceptibility weighted imaging; Vol, volumetric*

Supplementary Table 2. MRI sequences done in routine monitoring and relapse indications in MS patients

	3D IR-prep GE T1	2D T2 FLAIR	3D/Vol T2 FLAIR	2D Axial/Sagittal T1	2D Axial T2	3D Axial T2	2D Axial DWI	Pre-Gad 2D/3D Axial T1	Post Gad 2D/3D Axial T1	Axial 2D PD
Consortium	✓	✓	✓		✓	✓	✓		✓	
MAGNIMS		✓			✓				✓	
1		✓			✓		✓	✓	*	
2			✓		✓					
3		✓		✓	✓				✓	
4			✓	✓	✓		✓		*	
5			✓		✓		✓	*	*	
6		✓	✓		✓		✓	*	*	✓
7		✓		✓	✓		✓		*	
8			✓		✓		✓	*	*	
9			✓			✓		*	*	
10			✓	✓	✓		✓		*	
11			✓		✓		✓		*	
12		✓		✓	✓		✓		*	
13			✓		✓		✓	*	*	
14			✓		✓			*	*	
15		✓			✓			*	*	
16			✓		✓		✓		*	
17			✓			✓	✓		*	
18		✓			✓		✓	*	*	
19		✓			✓		✓		*	
20			✓		✓		✓	*	*	
21			✓		✓		✓		*	
22	✓		✓				✓		*	✓
23			✓	✓	✓		✓		*	
24	✓	✓			✓				*	
25		✓			✓		✓	*	*	✓

*✓, scan sequences are included routinely; *****, scan sequences are only included when requested by the clinician; 2D, two-dimensional; 3D, three-dimensional; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; Gad, gadolinium; GE, gradient echo; IR, inversion recovery; PD, proton density; Vol, volumetric*

Supplementary Table 3. MRI sequences done for PML surveillance in MS patients

	3D IR-prep GE T1	2D T2 FLAIR	3D/Vol T2 FLAIR	2D Axial/Sagittal T1	2D Axial T2	2D Axial DWI	Pre-Gad 2D/3D Axial T1	SWI	Post Gad 2D/3D Axial T1	Axial 2D PD
Consortium		✓	✓			✓				
MAGNIMS		✓	✓		✓	✓				
1		✓			✓	✓	✓		*	
2			✓		✓	✓				
3		✓		✓	✓	✓				
4			✓			✓				
5			✓			✓		✓		
6		✓	✓		✓	✓				
7		✓				✓		✓		
8			✓		✓	✓				
9			✓			✓				
10		✓			✓	✓				
11			✓		✓	✓			*	
12		✓		✓	✓					
13		✓			✓	✓				
14		✓			✓		*		*	
15		✓			✓		*		*	
16			✓		✓	✓				
17		✓		✓	✓	✓		✓		
18		✓			✓	✓				
19		✓			✓	✓				
20			✓		✓	✓				
21			✓	✓	✓	✓			*	
22			✓			✓				
23			✓			✓				
24	✓	✓			✓					
25		✓			✓	✓				✓

✓*, scan sequences are included routinely;* *******, scan sequences are only included when requested by the clinician; 2D, two-dimensional; 3D, three-dimensional; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; Gad, gadolinium; GE, gradient echo; IR, inversion recovery; PD, proton density; SWI, susceptibility weighted imaging; Vol, volumetric*