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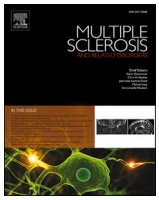

Quantifying the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis in the United Kingdom: A time and motion study

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ABSTRACT

Background: The treatment landscape for relapsing multiple sclerosis (MS) has changed dramatically in recent decades, including an increasing number of high-efficacy disease-modifying therapies (DMTs) with varied administration and monitoring requirements. Coupled with greater focus on earlier treatment, these factors have resulted in stretching of the capacity of MS specialist services and allied healthcare professionals (HCPs). To assist with the effective planning of MS services in the UK NHS, this study quantified the administration and monitoring time burden associated with high-efficacy DMTs (alemtuzumab, cladribine tablets, fingolimod, natalizumab, and ocrelizumab) for relapsing MS.

Methods: A Time and Motion (T&M) study was conducted across four MS centres in the UK, over 3–4 months per centre (Aug 2019–Feb 2021). Time dedicated by HCPs (including but not limited to neurologists, MS specialist nurses, infusion nurses, and healthcare assistants) to pre-specified drug administration and monitoring activities, elicited during pre-study interviews at each centre, was assessed for each of the selected DMTs. Administration activities included: installing peripheral access; pre-medication administration (if needed); preparing drug for infusion; infusion initiation, monitoring, and disconnection; and patient monitoring post-infusion. Monitoring activities included: booking appointments for blood draws; blood draw; retrieval and review of blood results; maintaining blood records and follow-up with the patient; checking availability of MRI results and follow-up with the patient; booking appointments for neurologist or nurse consultations; and checking patient files prior to clinic visits. A T&M model was built using observational T&M study results, data obtained through pre-study interviews, as well as stipulated monitoring intervals from relevant Summaries of Product Characteristics for the selected DMTs, to estimate active HCP time with each DMT, extrapolated over a period of 4 years per-patient.

Results: For oral DMTs, projected total active HCP time (monitoring only) per-patient over 4 years was 14.7 h for cladribine tablets and 19.2 h for fingolimod. For infused DMTs, total time (administration and monitoring) for alemtuzumab was 37.7 h (6.0 and 31.6 h, respectively), 48.1 h for natalizumab (17.4 and 30.8 h, respectively), and 23.5 h for ocrelizumab (6.1 and 17.4 h, respectively).

Abbreviations: COVID-19, coronavirus-19; CRF, case report form; DMT, disease-modifying therapy; GP, general practitioner; HCP, healthcare professional; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSSN, multiple sclerosis specialist nurse; NHS, National Health Service; NIHR, National Institute for Health and Care Research; OCT, optical coherence tomography; PLwMS, people living with multiple sclerosis; PSP, patient support programme; SD, standard deviation; SmPC, summary of product characteristics; T&M, Time and Motion; UK, United Kingdom.

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Conclusions: While active HCP time varied across centres, infused DMTs were projected to require the greatest amount of HCP time associated with administration and monitoring over 4 years versus oral DMTs. These findings may assist MS-specific HCPs in planning and delivering the equitable provision of DMT services for patients with relapsing MS.

1. Introduction

Over the last two decades, the treatment landscape for relapsing multiple sclerosis (MS) has evolved with new treatment paradigms and greater emphasis on earlier treatment with disease-modifying therapy (DMT) (Giovannoni, 2018; Hauser and Cree, 2020; Hartung et al., 2021). Whilst welcome, the greater focus on earlier treatment coupled with the increasing range and complexity of DMTs available, and their associated administration and monitoring requirements, is stretching the capacity of MS specialist services (MS Trust, 2016). A UK-wide audit in 2019, for example, highlighted the difficulty with management of higher-than-recommended caseloads and the significant variability in high-efficacy DMT prescribing rates across MS services and an average increase of 10 % in caseloads (Rog et al., 2021; Rog et al., 2021; Rog et al., 2021). Furthermore, a recent survey of 8,281 people living with MS (PLwMS) indicated a shortfall in accessibility to MS services across the UK (MS Society, 2019; MS Society, 2021). As expected, the onset of the Coronavirus-19 (COVID-19) pandemic intensified the pressures that MS services already faced in the UK and elsewhere (MS Society, 2021). Meanwhile, PLwMS undertaking treatment with DMTs are bearing the burden of the associated complex administration and monitoring schedules. The routine care involved varies according to the specific treatment used, largely depending on the treatment posology, administration route, and any safety considerations.

Taken together, these factors have led to MS healthcare professional (HCPs) placing a focus on ensuring the equitable provision of DMT services for PLwMS. This presents an ongoing challenge for MS services: how can they best utilise finite resources to support the drive for earlier and more effective DMT treatment, while still ensuring that all PLwMS receive appropriate, timely, and high-quality care?

To enable the effective planning of MS specialist services, there is a need to better understand the administration and monitoring burden of treatment with high-efficacy DMTs (defined by the Association of British Neurologists as "DMTs with an average relapse reduction substantially more than 50 %") (Scolding et al., 2015). Time and Motion (T&M) methodology has previously been used to measure the real-world time burden associated with healthcare processes across multiple therapeutic indications, (Body et al., 2017; De Cock et al., 2016; De Cock et al., 2016) and represents a suitable method to generate accurate measurements of the administration and monitoring burden associated with MS treatment; the ultimate goal being to improve the management of resources within MS healthcare facilities. The primary objective of this T&M study, therefore, was to estimate the administration and monitoring burden (time and cost) associated with selected high-efficacy DMTs (alemtuzumab, cladribine tablets, fingolimod, natalizumab, and ocrelizumab) for patients with relapsing MS in the UK. The secondary objectives were to estimate 1) the total active HCP time for MS-related administration and monitoring activities per patient over a 4-year period, and 2) the projected associated costs (HCP staff time, laboratory testing, and diagnostics) per patient over 4 years.

2. Methods

2.1. Study design and procedures

A prospective, observational T&M study was conducted across four MS centres in the UK. Standard T&M methodology, which consists of breaking down a process into discrete tasks (in this case, DMT-related administration and monitoring processes), and repeatedly measuring the duration of those tasks, was used (Lopetegui et al., 2014). Data were collected over a period of 3–4 months per centre, between August 2019 and February 2021, using generic Case Report Forms (CRF) and Activity Diary forms that were adapted to reflect local administration and monitoring workflows, respectively. The choice of data collection tool used (CRF or Activity Diary form) was guided by the nature of the data being collected.

Treatment-specific time data for infusion-related administration activities (Table 1) were collected by means of a CRF, with a target sample size of 10 observations each for alemtuzumab, natalizumab, and ocrelizumab infusion processes, per centre. A CRF tool was chosen because infusion-related activities occur sequentially at the same location (i.e., infusion suite). Primary outcome measures were: mean *active* HCP time per pre-defined administration task; mean total active HCP time for all infusion tasks combined; and mean chair time per single infusion. Time was measured and recorded by external observers. The HCPs who were observed included infusion nurses and healthcare assistants.

Time data were also collected for monitoring activities related to DMT treatments (with a target sample size of 10 observations per

Table 1
Pre-specified administration and monitoring tasks.

Administration tasks (target samples of 10 observations per infused DMT per centre)	Monitoring tasks (target samples of 10 observations per activity per centre; non-drug specific)
• Installing peripheral access • Pre-medication administration (if needed) • Prepare drug for infusion • Infusion initiation • Patient monitoring during infusion • Infusion disconnection • Patient monitoring post infusion	• Book appointment for blood draw • Blood draw • Retrieval and review of blood results • Dictate blood results letter • Type blood results letter • Review and approve blood results letter • Review of abnormal blood results • Check availability of MRI results • Dictate MRI results letter • Type MRI results letter • Review and approve MRI results letter • Book appointment for neurologist or nurse consultation visit • Check patient files prior to clinic visit

DMT, disease-modifying therapy; MRI, magnetic resonance imaging.

Table 2
Time and Motion model assumptions.

Work flow	Selected DMTs*	Assumption	Reason for assumption
Neurologist consultation visit	All	Baseline neurologist consultation visit is excluded	This visit is the same for all patients; the model accounts for administration and monitoring activities that are triggered by the decision regarding which DMT a patient will receive
Urine sample collection, standard blood count, and virology tests	All	Baseline tests are included	Small differences in baseline testing were reported depending on the DMT chosen (e.g., lower expected likelihood of urine sample collection for cladribine tablets, higher expected likelihood of thyroid function test for alemtuzumab, higher expected likelihood of JCV test for natalizumab, higher expected likelihood of immunoglobulin test for ocrelizumab)
MRI monitoring Cardiac and OCT monitoring	All Fingolimod	Time for performing diagnostic investigations (e.g., ECG, MRI, OCT) or visits to other specialists outside the MS department (e.g., ophthalmologist, GP) is excluded	To evaluate the time impact of different DMTs on MS-specific services only
Neurologist and MS nurse consultation visits	Alemtuzumab, natalizumab	No *ad hoc* blood draws are performed for alemtuzumab or natalizumab	Blood samples are already collected per routine monthly schedule
Blood monitoring	Alemtuzumab, natalizumab	Letters reporting blood test results are generated for only half the monthly bloods appointments for alemtuzumab and natalizumab	Based on expert feedback indicating that, with cases of monthly blood monitoring for alemtuzumab and natalizumab, results letters are not always generated (i.e., only when results for specific tests such as JCV are available)
Study year (DMT)	**Selected DMTs***	**Assumption**	**Reason for assumption**
Years 1–4	All	No treatment switches, discontinuations, or deaths occurred	To simplify the model and facilitate descriptive comparisons of active HCP time dedicated to different DMTs
Years 3–4	All	Neurologist and nurse consultations have same frequency as in Year 2	
Years 3–4	Alemtuzumab, cladribine tablets	No drug administration	
Years 3–4	Alemtuzumab	Same blood/MRI monitoring frequency as in Year 2	
Years 3–4	Cladribine tablets	Routine blood monitoring is not required, unless patient has low lymphocyte count [model assumes 5.1 % likelihood Giovannoni et al. (2018)]. Same MRI monitoring frequency as in Year 2	
Years 3–4	Fingolimod	Same blood/MRI monitoring frequency as in Year 2	
Years 3–4	Natalizumab, ocrelizumab	Same drug administration and blood/MRI monitoring frequency as in Year 2	
Years 3–4	Fingolimod	No cardiac or OCT monitoring	

*Selected DMTs included alemtuzumab, cladribine tablets, fingolimod, natalizumab, and ocrelizumab.
DMT, disease-modifying therapy; ECG, electrocardiogram; GP, general practitioner; HCP, healthcare professional; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCT, optical coherence tomography.

activity per site; Table 1). Activity Diary forms were preferred because the activities were non-drug specific (i.e., the same irrespective of the DMT used), independent of each other (i.e., could be carried out by different types of HCPs at different locations and take place at unpredictable times), and could be performed for multiple MS patients simultaneously. Primary outcome measures were mean active HCP time per pre-defined monitoring task (recalculated to a single patient). Time was self-reported by HCP's and recorded onto the Activity Diary form. HCPs for which time data were collected included (but were not limited to): neurologists; MS specialist nurses (MSSNs); and administrative staff.

A post-study interview was performed to obtain real-world frequencies of monitoring events (blood draws, magnetic resonance imaging (MRI) scans, other diagnostic investigations), the types of laboratory analyses performed, and the frequency and duration of neurologist and MSSN clinic visits.

A Time and Cost model was built to estimate the active HCP time and cost associated with each DMT, extrapolated over a period of 4 years. The model used as its core inputs the mean time for each pre-specified task, dosing information from the relevant Summary of Product Characteristics (SmPC), (Aventis Pharma Limited, 2022; Biogen Netherlands B.V., 2022; Merck Serono Limited, 2022; Novartis Pharmaceuticals UK Limited, 2022; Roche Products Limited, 2021), real-world frequencies of monitoring events, laboratory testing, and consultation visits as obtained from the pre-and post-study interviews, and publicly available unit costs for relevant HCP staffing levels (Curtis and Burns, 2020; Curtis and Burns, 2019).

The model incorporated multiple (often conservative) assumptions, the rationale for which is described in Table 2. For alemtuzumab and cladribine tablets, the model accounted for SmPC dosing guidance indicating that both treatments are only administered in Year 1 and Year 2 (i.e., not in Years 3 and 4) (Aventis Pharma Limited, 2022; Merck Serono Limited, 2022). Time taken to conduct tests deemed ancillary to the core MS team, such as MRI scans, cardiac monitoring, and optical coherence tomography (OCT), were not included in the analysis. However, tariffs of these investigations, including estimated costs for performing laboratory analyses, were included in the cost model. In addition to the assumptions detailed in Table 2, we assumed that the time for all the pre-specified blood monitoring and MRI-related tasks could be applied to the blood and MRI monitoring frequency, respectively, irrespective of location of blood draw (hospital, peripheral clinic, or GP practice) or MRI (hospital or peripheral clinic), type of blood draw or MRI (routine or *ad hoc*), or type of blood draw or MRI result (normal or abnormal). Finally, time taken to perform administrative tasks related to cardiac and OCT monitoring (i.e., preparing and reviewing results letters) were estimated from timings collected for the MRI-related tasks.

It should be noted that, for oral DMTs, HCP-supervised administration of tablets, as well as tasks associated with patient support programmes (PSPs), were not included in the model. Regarding the administration of tablets, it was expected that this requires no or minimal HCP oversight. Tasks related to PSPs are mainly performed by home care companies and were therefore considered outside the remit of this study (i.e., time not dedicated by MS unit personnel). HCPs across the four sites noted that PSPs run by home care companies function generally satisfactorily and administrative tasks related to managing PSPs at the MS centres occur very infrequently.

A description of the procedures involved in this study is available in the **Supplementary Methods.**

2.2. Statistical analysis

This was a descriptive, non-hypothesis testing study; therefore, no formal sample size calculation was performed. The target sample size for the administration process of alemtuzumab, natalizumab, and ocrelizumab was 10 infusion observations per drug. Given that no treatment-specific data were collected to measure monitoring time burden, a sample of 10 measurements per task was considered adequate to capture within-centre variability in workflow and associated time.

Descriptive statistics were calculated as mean, standard deviation (SD), median, and 95 % confidence intervals for continuous variables, specifically active HCP time for each pre-specified monitoring task and total active HCP time for all pre-specified administration tasks combined, per DMT infusion observation. Analyses were run by centre and pooled for all centres combined. For the pooled analysis of time-related endpoints, a mixed model was used with centre as random intercept effect to better capture between-centre variability.

All data were analysed using SAS© version 9.4.1 (SAS Institute Inc., Cary, NC, USA). Mean values of pooled data across the four centres are presented; minimum and maximum values reflect the results for individual centres.

2.3. Time and cost model

The Time and Cost model was built in Microsoft Office 365® Excel® and was used to calculate estimated active HCP time and cost associated with each DMT per patient per year for each centre, and for all four centres combined (Years 1–4 and all 4 years combined).

Estimated administration-related active HCP time per patient over 4 years was calculated by:

1. Multiplying the mean administration-related active HCP time per infusion for each DMT by the relevant SmPC recommended administration frequency for Years 1–4 (see Fig. 2 for details concerning annual administration frequency of each DMT).
2. Calculating the sum of administration-related active HCP time per patient over the 4 years.

Estimated monitoring-related active HCP time per patient over 4 years was calculated by:

1. Multiplying the mean time taken to complete each task by the probability of that task occurring.
2. Multiplying the resulting value by the average frequency of performing each task in years 1–4 (determined by centre interviews and guided by SmPC recommendations).
3. Calculating the sum of monitoring-related active HCP time per patient over the 4 years.

The model quantified the opportunity cost of active HCP time. To transfer HCP time to cost, the cost per minute for each staff type was derived from UK public sources (Curtis and Burns, 2020; Curtis and Burns, 2019). The estimated cost burden of each DMT per patient over 4 years was subsequently estimated by combining the opportunity cost of active HCP time (observational time data) and estimated costs of laboratory and diagnostic tests using publicly available cost data (see **Supplementary Table S1**).

2.4. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the Health Research Authority on 14 May 2019; for the centre based in Scotland, approval was granted by Research and Development NHS Highlands on 25 October 2019. Neither submission to an Ethics Committee nor patient/HCP consent was required because of the nature of the study, since no patient-identifying data were collected. The study was included in the National Institute for Health and Care Research (NIHR) Clinical Research Network Portfolio (however, NIHR support was utilised at the Scottish-based centre only).

2.5. Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

3. Results

3.1. Centre-specific interviews

Relevant outcomes from the centre-specific semi-structured interviews, which were conducted prior to study commencement to help elucidate the 'core' sets of tasks involved in the different workflows and that were also conducted post-data collection completion to inform the assumptions in Table 2, are described in the **Supplementary Results**.

3.2. Administration-related active HCP time

The number of administration-related observations collected for alemtuzumab, natalizumab, and ocrelizumab at each centre are reported in Table 3. Data for infused DMTs were only reported for three out of four centres due to the COVID-19 pandemic.

Mean (minimum; maximum) chair time per infusion across centres was 267.5 (224.8; 318.6) min (Fig. 1). This varied between the DMTs and, in order of highest to lowest, was: 449.6 (322.6; 590) min for alemtuzumab, 266.3 (234.8; 294.5) min for ocrelizumab, and 86.6 (71.3; 106.1) min for natalizumab. The differences in mean chair time between DMTs were largely driven by variation in the mean time spent in the chair *prior* to infusion initiation, including pre-medication (ranging from 18.1 min with natalizumab to 192.1 min with alemtuzumab) and infusion duration (ranging from 65.3 min with natalizumab to 251.2 min with alemtuzumab).

Mean (minimum; maximum) active HCP time per infusion across centres was 36.2 (27.8; 44.1) min (Fig. 1). This varied between DMTs and, in order of highest to lowest, was: 45.2 (31.4; 54.6) min for alemtuzumab, 40.9 (27.1; 58.9) min for ocrelizumab, and 20.0 (14.9; 25.7) min for natalizumab. The differences in mean active HCP time between DMTs were largely due to variation in the time actively dedicated to patient monitoring during the infusion (ranging from 1.2 min with natalizumab to 14.0 min with alemtuzumab).

During the data collection period, no infusion reactions were recorded; therefore, time dedicated to the management of an infusion

Table 3
Infusion-related observations reported per centre,* by infused DMT.

Infused DMT	Centre 1	Centre 2	Centre 3	Total observations
Alemtuzumab	10	4	8	22
Natalizumab	10	10	10	30
Ocrelizumab	10	18	10	38
Total observations	30	32	28	90

*The remaining centre is not shown because no observations were completed due to the COVID-19 pandemic.
DMT, disease-modifying treatment.

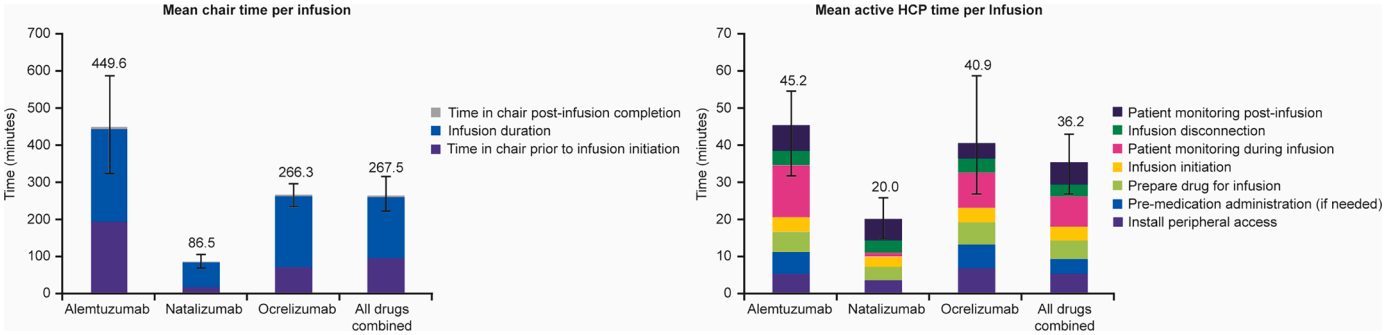

Fig. 1. Mean chair time and mean active HCP time dedicated per infusion.
Error bars signify the range of values, across the three centres that contributed data.
HCP, healthcare professional.

reaction was not factored into the analysis.

Administration-related active HCP time for each treatment was subsequently extrapolated over a 4-year time period, based on SmPC recommendations. Mean (minimum; maximum) administration-related active HCP time was estimated to be (highest to lowest) 17.4 (12.9; 22.2) h for natalizumab, 6.1 (4.1; 8.8) h for ocrelizumab, and 6.0 (4.2; 7.3) h for alemtuzumab (Fig. 2).

3.3. Monitoring-related active HCP time

The number of monitoring-related observations per centre-specific task are presented in **Supplementary Table S2**, while **Supplementary Table S3** shows the mean active HCP time taken to complete tasks related to pre-specified monitoring activities and the related probabilities used in the model. Finally, **Supplementary Table S4** shows the average yearly frequency of pre-specified monitoring tasks by DMT.

Mean active HCP time per task and average annual task frequency were used to estimate monitoring-related active HCP time dedicated to each patient over a 4-year period for each treatment (Fig. 3). Estimated mean (minimum; maximum) monitoring-related active HCP time per patient over 4 years, ordered highest to lowest, was: 31.6 (22.5; 38.2) h for alemtuzumab, 30.8 (21.5; 34.7) h for natalizumab, 19.2 (13.5; 22.4) h for fingolimod, 17.4 (12.3; 20.0) h for ocrelizumab, and 14.7 (11.2; 16.4) h for cladribine tablets. Differences in monitoring-related active HCP time between treatments were largely driven by time dedicated to blood monitoring activities (ranging from 2.4 h with cladribine tablets to 17.8 h with alemtuzumab) and infusion-related administrative tasks (ranging from 0 h with cladribine tablets and fingolimod to 8.4 h with natalizumab).

Yearly number of DMT infusions according to SmPC recommendations

Study year	Alemtuzumab*	Natalizumab	Ocrelizumab
Year 1	5	13	3
Year 2	3	13	2
Year 3	0	13	2
Year 4	0	13	2

Infusion-related active HCP time per patient over 4 years

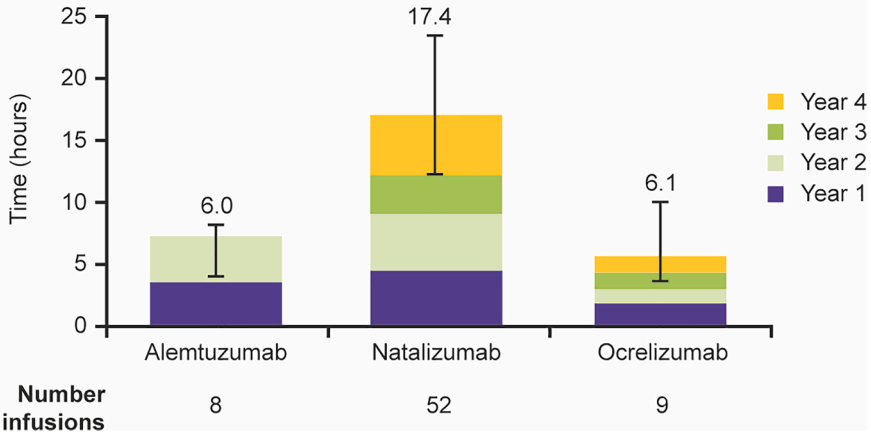

Fig. 2. Estimated infusion-related active HCP time per patient by DMT over 4 years, guided by SmPCs.
*The model assumed that there were no alemtuzumab infusions in Years 3 and 4 (see Table 1).
Error bars signify the range of values, across the three centres that contributed data. Yearly number of DMT infusions were deduced from the DMTs' respective SmPC's: alemtuzumab (Aventis Pharma Limited, 2022), natalizumab (Biogen Netherlands B.V, 2022), and ocrelizumab (Roche Products Limited, 2021). DMT, disease-modifying treatment; HCP, healthcare professional; SmPC, Summary of Product Characteristics.

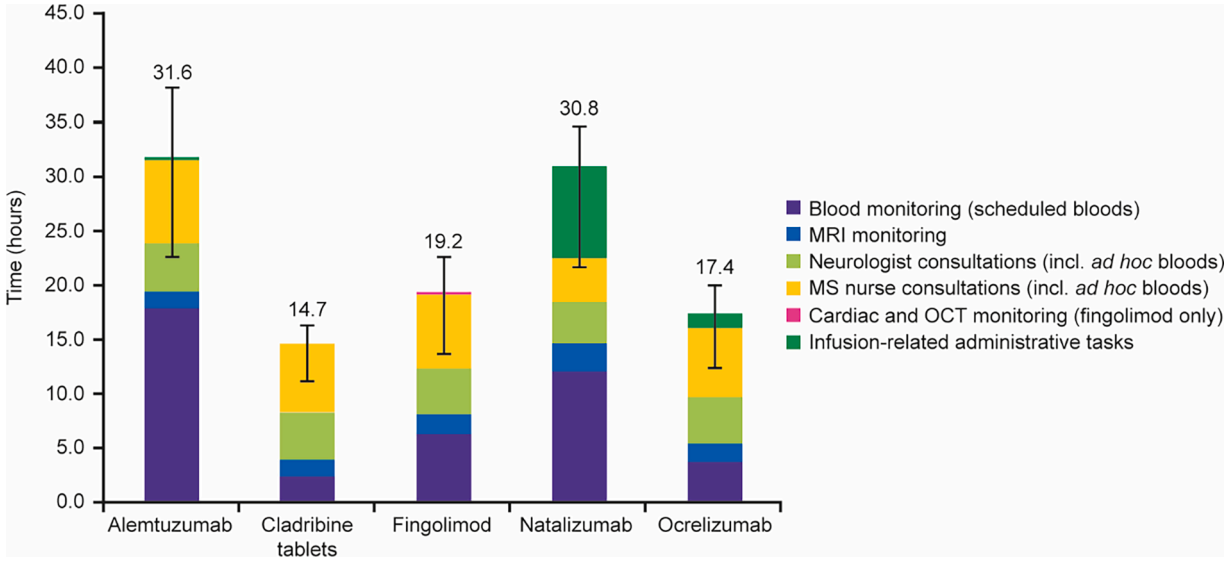

Fig. 3. Estimated monitoring-related active HCP time per patient, by DMT, over 4 years.
Error bars signify the range of values, across the four participating centres.
MS, multiple sclerosis; MRI, magnetic resonance imaging; OCT, optical coherence tomography.

3.4. Total active HCP time

Estimated total active HCP time dedicated to administration and monitoring activities combined over a period of 4 years, ordered highest to lowest, was: 48.1 h with natalizumab, 37.7 h with alemtuzumab, 23.5 h with ocrelizumab, 19.2 h with fingolimod, and 14.7 h with cladribine tablets (Fig. 4).

3.5. Administration and monitoring-related costs associated with selected DMTs

Estimated mean total costs (including administration and monitoring costs, as well as costs for laboratory testing and diagnostic investigations, excluding day case tariff costs to administer DMTs) per patient over 4 years, ordered highest to lowest, were £5,283 with alemtuzumab, £4,755 with natalizumab, £3,071 with fingolimod, £2,593 with ocrelizumab, and £2,197 with cladribine tablets (Fig. 5).

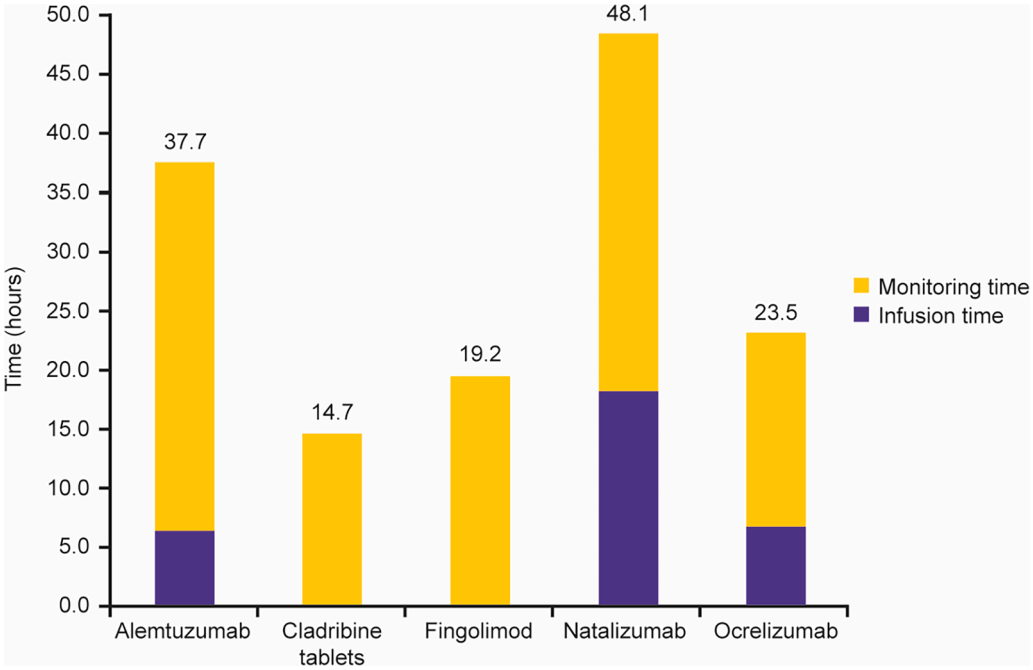

Fig. 4. Estimated total active HCP time per patient, by DMT, over 4 years.
Note: In the majority of centres, the types of HCP involved in administrating and monitoring the DMTs differ according to the task being performed.
DMT, disease-modifying treatment; HCP, healthcare professional.

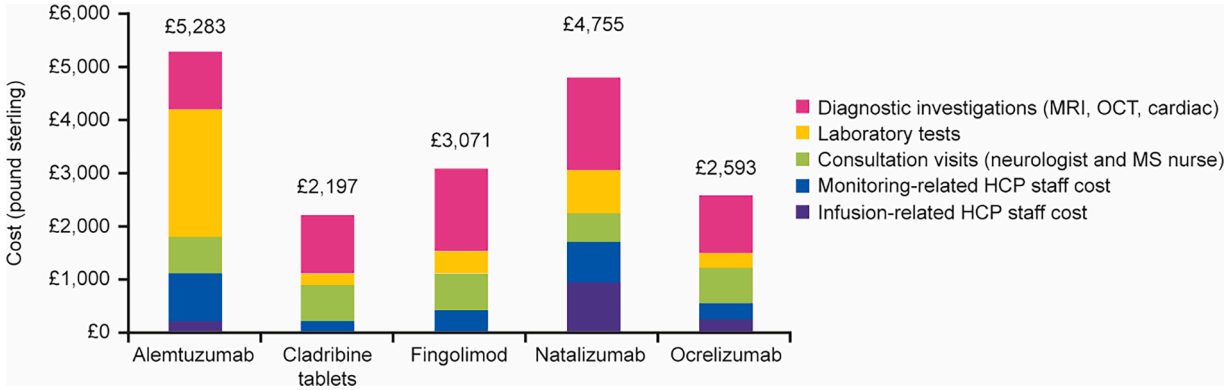

Fig. 5. Estimated total administration- and monitoring-related costs per patient, by DMT, over 4 years.
Staff time was transformed into costs using salary data from 2020 PSSRU data; diagnostic unit costs were estimated using data from the National Cost Collection: National Schedule of NHS Costs (2018-2019) and the cost of laboratory tests were estimated using data from the National Cost Collection: National Schedule of NHS costs (2018-2019) and NICE data sources (guidance TA312, PH43, NG33, NG60). Costs of day case tariffs to administer DMTs were not included.
DMT, disease-modifying treatment; HCP, healthcare professional; MS, multiple sclerosis; MRI, magnetic resonance imaging; OCT, optical coherence tomography.

4. Discussion

We believe this to be the first study to use T&M methodology to map administration and monitoring workflows in the setting of high-efficacy DMTs in relapsing MS, with the aim to quantify active HCP time and associated opportunity costs. Conducted across four MS specialist centres in the UK, results showed that infused DMTs were projected to require the greatest amount of active HCP time and cost associated with administration and monitoring over 4 years versus oral DMTs, with cladribine tablets requiring the lowest amount of time. While the results are not entirely unexpected, this quantification of the time and costs associated with each DMT could be used by MS specialist centres in the UK to inform and plan the effective management and delivery of their DMT services, with a view to improving efficiency. The study does not aim to advise on which treatment(s) should be used – this should be based on the benefit-risk profile of individual patients – but quantifies the impact upon resource of treatment approaches.

In recent years, there has been an increasing demand on MSSN time, largely owing to the rising numbers of PLwMS and the complexity of the administration and monitoring of the DMTs prescribed (MS Trust, 2021). In 2021, the MS Trust suggested that the recommended sustainable caseload for MSSNs in UK should be reduced from 358 to 315 (MS Trust, 2021; Punshon et al., 2021). However, data indicate that MSSNs in the UK are substantially overstretched (Rog et al., 2021; MS Trust, 2021). A 2021 MS Trust survey estimated that 79 % of PLwMS come from areas where MSSN caseloads are unsustainable, and suggested that a doubling in the current number of MSSNs is needed across the UK (MS Trust, 2021). To help deliver optimal patient care and ensure DMT services are available in equal measure to all PLwMS across the UK, it is vital that UK MS centres are appropriately equipped with the tools to manage the administration and monitoring time burden associated with their demanding caseloads. The results of this study should help to engage commissioners to recognise these issues.

This study highlights an opportunity to learn from centre-based variation in MS care, in terms of where efficiencies could be made. For example, physicians at some centres may see fewer patients due to the large amount of time dedicated to administrative tasks (such as preparing and reviewing clinic letters and reviewing blood/MRI results). Reducing the frequency and reallocating some of these tasks, where possible, and improving digital integration, could allow for more patients to be treated within the same time span.

The estimated total administration- and monitoring-related costs per patient by DMT over 4 years largely correlated with the amount of active HCP time dedicated per patient. While active HCP time varied across centres, the trends in administration- and monitoring-related active HCP time by DMT were similar, supporting the robustness of the findings. Unsurprisingly, alemtuzumab and natalizumab were associated with the highest costs and cladribine tablets were associated with the lowest costs. Alemtuzumab was projected to have the highest estimated costs per patient, noticeably owing to the higher frequency of risk mitigation laboratory tests required in patients receiving this treatment. For natalizumab, increased costs were driven by higher infusion-related HCP staff costs as well as those related to diagnostic investigations (i.e., MRI).

Centre variability in cost per patient was greatest for natalizumab, which was largely explained by between-centre differences in projected infusion-related HCP staff costs. Specifically, this was largely due to differences in workflows, i.e., the need or not for 1) the HCP to check the patient file prior to an infusion, 2) the HCP to book the appointment for the next infusion, and 3) the HCP to communicate the appointment to the patient, the related time for each task, and the type of HCP performing each task and associated hourly rate (e.g., one site had a more pharmacy-led service). Such findings could provide a learning opportunity to optimise infusion-related processes between centres. While the study concentrated on *active* HCP time expended in the administration of infused DMTs, it also aimed to quantify *total* chair time spent in the infusion unit (which is the principal measure of MS centres' physical capacity to deliver these treatments). Average chair time duration was greatest for alemtuzumab, followed by natalizumab and ocrelizumab, respectively. Variation in mean chair time between centres was largely due to differences in chair time *prior* to infusion initiation.

Since the cost analysis only focused on the administration- and monitoring-related costs incurred per patient, calculations did not include the cost of the drug, the day case tariff to administer the drug, or the cost of consumables. As per the Methods, costs associated with the HCP-supervised administration of tablets, as well as PSPs, were also not incorporated. The analysis included a combination of the opportunity cost (HCP time multiplied by salary cost) and tariffs for diagnostics (e.g., MRI scans and cardiology assessments) as a proxy for the time taken to perform the investigations. As such, cost estimates do not fully reflect hospital funding of MS patients, which was outside the remit of this study.

The results presented in this T&M study are conservative but deemed robust. This approach is reflected in the assumptions (e.g., no *ad hoc* blood draws are included for alemtuzumab or natalizumab; time for performing diagnostic investigations or visits to other specialists outside the MS department is excluded; no cardiac or OCT monitoring with fingolimod in Years 3 and 4), resulting in a likely underestimation of the active HCP time and costs associated with the respective DMTs, and giving no comparative advantage to cladribine tablets. The use of SmPC-recommended dosing frequency to calculate administration-related

active HCP time per infused DMT over 4 years, also adds methodological robustness.

The study was also subject to a number of limitations. The study reflects the overall situation in four UK MS centres, some of whom collected data in the COVID-19 pandemic, and may not be generalisable to the whole of the UK, even though selected centres were geographically dispersed across the UK and presented different caseloads. Also, given the complexity of the processes involved, it was not possible to accurately capture all steps associated with the monitoring of MS patients in the workflows. Therefore, actual active HCP time dedicated to monitoring is underestimated in this study. However, via pre-study interviews, a core set of tasks was initially identified that were considered the main contributors towards total monitoring time. Those tasks were common to all sites, enabling data pooling to generate meaningful analyses. In addition, administration-related observation targets were not met for all DMTs studied, due, for example, to a pause in the use of alemtuzumab during the COVID-19 pandemic at one of the centres. No observations were collected for some pre-specified administrative monitoring-related activities that were included in the Activity Diary (e.g., chasing up diagnostic results, sending letters with blood results to patients, and preparing list of patients due for infusion). Such activities were either not performed routinely or took place in different locations of the MS unit, and were outside the immediate supervision of the site's study coordinator.

As noted, the present study straddled the COVID-19 pandemic, and the way in which DMTs were prescribed in the UK changed during this time (Williams et al., 2022). This may have been related to concerns about response to COVID-19 vaccination among those receiving certain DMTs, (Garjani et al., 2022) although data from the UK MS register indicated that COVID-19 outcomes were generally similar (Middleton et al., 2021). Despite this, the participating sites confirmed that the processes around high efficacy drug administration and monitoring remained largely unchanged during the COVID-19 pandemic, and continued to reflect standard practice.

Lastly, it should be noted that patients receiving alemtuzumab may also require a third infusion within the first 4 years, while patients on natalizumab may need increased MRI surveillance for progressive multifocal leukoencephalopathy in Years 3 and 4 (depending on JCV status). However, such scenarios were not accounted for. The model also assumed no treatment switches or discontinuations during the 4-year timeframe, to facilitate descriptive comparisons between the DMTs.

5. Conclusions

While active HCP time varied across centres, infused DMTs were projected to require the greatest amount of active HCP time associated with administration and monitoring over 4 years versus oral DMTs, with cladribine tablets requiring the lowest amount of time. The model and data presented in this T&M study may therefore act as a useful resource for MS specialist centres in the UK, serving to inform the effective planning of DMT services with a view to enhancing the equitable provision of treatments.

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CRediT authorship contribution statement

David Rog: Conceptualization, Methodology, Supervision, Investigation, Project administration, Writing – review & editing. **Wallace Brownlee:** Methodology, Investigation, Project administration, Writing – review & editing. **Francisco Javier Carod-Artal:** Methodology, Investigation, Project administration, Writing – review & editing. **Seema Kalra:** Methodology, Investigation, Project administration, Writing – review & editing. **Noreen Barker:** Investigation, Writing – review & editing. **Claire Lowndes:** Investigation, Writing – review & editing. **Jessica Pendlebury:** Investigation, Writing – review & editing. **Stephanie Leclerc:** Investigation, Writing – review & editing. **Amerah Amin:** Conceptualization, Methodology, Project administration, Visualization, Writing – review & editing, Funding acquisition. **Luke Ashton:** Conceptualization, Methodology, Project administration, Visualization, Writing – review & editing, Funding acquisition. **Hannah Evans:** Conceptualization, Methodology, Project administration, Visualization, Writing – review & editing, Funding acquisition. **Erwin De Cock:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing – review & editing, Writing – review & editing.

Declaration of competing interest

DR has received honoraria from Biogen, Celgene (BMS), Hikma, Janssen, MedDay, Merck, Novartis, Roche, Sandoz, Sanofi, and Teva. WB has received honoraria from Biogen, Celgene (BMS), Merck, Mylan, Novartis, Roche, Sanofi, and Viatris. FJC-A has received honoraria and/or travel grants from BMS, GW, Janssen, Merck, Novartis, and Roche. SK has received honoraria from Biogen, Merck, Novartis, and Sanofi. NB has received honoraria and support to attend conferences from: Biogen, Merck, Novartis, Sanofi, Roche, and Teva. CL has received an honorarium from Merck and support from Biogen to attend a meeting. JP has nothing to disclose. SL and EDC are employees of Syneos Health. AA, LA, and HE are employees of Merck Serono Ltd, Feltham, UK, an affiliate of Merck KGaA.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.105380.

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