ORIGINAL RESEARCH ARTICLE

# ENTIMOS: A Discrete Event Simulation Model for Maximising Efficiency of Infusion Suites in Centres Treating Multiple Sclerosis Patients

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## Abstract

**Background**  Improved multiple sclerosis (MS) diagnosis and increased availability of intravenous disease-modifying treatments can lead to overburdening of infusion centres. This study was focused on developing a decision-support tool to help infusion centres plan their operations.

**Methods**  A discrete event simulation model ('ENTIMOS') was developed using Simul8 software in collaboration with clinical experts. Model inputs included treatment-specific clinical parameters, resources such as infusion chairs and nursing staff, and costs, while model outputs included patient throughput, waiting time, queue size, resource utilisation, and costs. The model was parameterised using characteristics of the Charing Cross Hospital Infusion Centre in London, UK, where 12 infusion chairs were deployed for 170 non-MS and 860 MS patients as of March 2021. The number of MS patients was projected to increase by seven new patients per week.

**Results**  The model-estimated waiting time for an infusion is, on average, 8 days beyond clinical recommendation in the first year of simulation. Without corrective action, the delay in receiving due treatment is anticipated to reach 30 days on average at 30 months from the start of simulation. Such system compromise can be prevented either by adding one infusion chair annually or switching 7% of existing patients or 24% of new patients to alternative MS treatments not requiring infusion.

**Conclusion**  ENTIMOS is a flexible model of patient flow and care delivery in infusion centres serving MS patients. It allows users to simulate specific local settings and therefore identify measures that are necessary to avoid clinically significant treatment delay resulting in suboptimal care.

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**Key Points for Decision Makers**

The operations of infusion centres that serve multiple conditions, including multiple sclerosis, can be simulated through a discrete event simulation (DES) model with reasonable apparent accuracy.

A DES model that maximises the efficiency of an infusion suite can help inform decision making about healthcare resource allocation.

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# 1 Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, affecting an estimated 2.2 million people worldwide [1, 2]. The prevalence of MS is steadily rising as diseased patients live longer. In the UK alone, the prevalence of MS increased by 29% between 1990 and 2016, reaching 106,454 patients, with 130 new cases diagnosed each week [3, 4]. Although MS is currently incurable, several disease-modifying therapies (DMTs) exist for relapsing forms of MS (RMS) [5].

Currently approved MS DMTs include immunomodulatory and anti-inflammatory drugs [6] administered orally as subcutaneous injectables or as intravenous infusions over multiple cycles [7]. DMTs can be categorised depending on their degree of efficacy in preventing relapses; however, identifying DMTs for treatment is based on medical or financing guidelines and the patient's perception of risks [8]. Currently, the treatments recognised to have the highest impact on relapse activity include alemtuzumab, natalizumab, and ocrelizumab. All these treatments are administered as infusions in specialist infusion centres under clinical supervision, as per their summary of product characteristics (SmPC).

Infusion centres serve patients with neurological diseases and other conditions (e.g., oncological and rheumatological) with finite resources, putting them at risk of being overburdened. Literature indicates that infusion centres commonly experience long waiting times: the time from treatment decision to administration, and waiting times from patient arrival until start of infusion [9]. This can lead to suboptimal clinical outcomes and patient dissatisfaction [9, 10]. Delays in treatment administration warrant more effective short-term resource utilisation.

The waiting time and queue size in infusion centres are influenced by capacity constraints, such as the number of available infusion chairs and available staff, scheduling techniques, time taken from patient's arrival to infusion start, last-minute additions or appointment cancellations, and time taken to manage infusion-related adverse events [9, 11]. Other factors that impact waiting time and queue size include patient resistance to treatment decision and insurance-related issues [12–14]. Finally, external unexpected circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, place centres under further strain. This impacts several constraints related to scheduling, chair capacity, implementation of additional COVID-related screening, additional cleaning and disinfection activities between infusions, and extended working hours [15].

Infusion-related capacity constraints are well-studied in other therapeutic areas, including oncology, but are not well-characterised in MS [16, 17]. Adopting appropriate resource modelling techniques may allow for improved capacity constraint management. Thokala et al. defined resource modelling as the quantitative assessment of technology diffusion curves, their related resource requirements, and their capacity constraints [11]. The authors prescribe studies utilising discrete event simulation (DES) modelling techniques, which provide estimates of resource use and availability over time of a given service setting [11, 18]. Given the complexity of real-life clinical settings, it is crucial to develop the most parsimonious model, which would simultaneously allow for simplicity, relevance, and high predictive power.

This paper describes a model called ENTIMOS (meaning 'genuine', 'honest' in Greek) developed using Simul8[®][1] DES software (Simul8 Corporation) to maximise the efficiency of an infusion suite based on the most appropriate allocation of system resources. In particular, the model simulates the time and resource utilisation associated with three intravenously administered DMTs for MS, viz. ocrelizumab, natalizumab, and alemtuzumab [19–21], and patient waiting time associated with their administration. The infusion pathway and input parameters can be adjusted in the model to reflect the situation in a particular infusion centre, and a case study is presented in this study using data from Charing Cross Hospital in London, UK. We discuss the benefits of using this model for patients, healthcare providers and payers, reflecting also on its generalisability, adaptability and limitations.

# 2 Materials and Methods

## 2.1 Conceptual Modelling

Qualitative information regarding MS infusion pathways was collected from infusion centres serving MS patients across the US and UK. Centres were identified as part of a parallel prospective study (unpublished) focusing on understanding the details of the infusion process in various countries. In the US, 13 centres were contacted by email, of which six responded, while in the UK, three centres were contacted, of which two responded. A larger number of centres were needed in the US to identify variations in process flows, whereas the two UK centres are nationally representative of large infusion centres according to the clinicians interviewed. Site administrators, nurses and pharmacists at the selected centres were requested to complete three separate questionnaires between April and July 2020. Different aspects investigated for each respondent type are detailed in Table 1. Information from the sites was summarised as a single common model process flow, whose clinical accuracy was validated by a clinical neurologist in the UK.

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[1] Simul8[®] is a registered trademark of Simul8 Corporation.

**Table 1** Data collected at infusion centres to develop process flow

| Respondent | Information |
|---|---|
| Site administrators | Site setup |
| | No. of infusion chairs/beds |
| | No. of staff (neurologists/nurses/pharmacists) |
| | Patients served by site |
| | Types of patients (MS/non-MS) accommodated |
| | No. of patients |
| | MS vs. non-MS |
| | For MS patients: no. of patients taking ocrelizumab, natalizumab or alemtuzumab |
| | Billing |
| | Cost of infusion (fixed/variable) |
| | Cost of administration (fixed/variable) |
| | Surcharges, if applicable |
| | Billing for concomitant medication (included in cost of infusion/separate from cost of infusion) |
| | MS infusion-related processes |
| Nurses | Organisation of work in centre (by patient/by task) |
| | Average hours allocated to patient care |
| | Infusion process workflow: which tasks are conducted and in what order |
| Pharmacists | Preparation of MS IV DMTs |
| | Bulk preparation per day/per patient |
| | Preparation of premedication |
| | Amount of time needed to prepare MS IV DMTs and premedication |

*DMTs* disease-modifying therapies, *IV* intravenous, *MS* multiple sclerosis

This process flow was used as the conceptual modelling framework for ENTIMOS. Given the degree of variation across infusion centres, the model combines common elements across the process flows with both conditional statements (i.e., if-else/case-type constructs), and user customisation options. The case study in this paper uses information on site processes provided by Charing Cross Hospital.

The ENTIMOS model was implemented in Simul8, a proprietary DES software [22].

## 2.2 Process Flow

Figure 1 depicts the process flow of the model, while the model interface and visual settings are presented in Fig. 2 (electronic supplementary material [ESM] 4 includes the study figures). In the model, as MS DMT is prescribed, providing pharmacies must approve treatment reimbursement before scheduling the first infusion appointment. The time to hospital pharmacy approval is assumed to vary between 4 and 20 weeks, as per the hospital pharmacist information. Once the patient's appointment is scheduled, laboratory tests must be performed to rule out contraindications for treatment (e.g., active hepatitis B virus infection), followed by vital signs checks and patient screening as well as optional oral pretreatment. Users can decide whether these happen ahead of time outside of the clinic (default) versus in a waiting room or in an infusion chair. On the day of the infusion, patients check in to the clinic and receive pretreatment with

intravenous anti-inflammatory drugs. Thereafter, MS DMT is administered as per their SmPC or the centre's standard operating procedures (SOPs). Handling of any infusion-related reactions (IRRs) is determined based on type and severity, and includes stop, slowdown infusion, or slowdown with symptomatic treatment. Following infusion, a patient is monitored over a prescribed period, which varies across DMTs as per the centre's SOP. Default durations of each of these processes are listed in ESM Table 1. These values were based on responses provided in the qualitative evaluation, by a clinical neurologist, or subsequently from literature, unless otherwise indicated. Patient resistance to treatment and insurance-related issues are currently not considered in this model.

## 2.3 Input Parameters

### 2.3.1 Patient Mix

Model inputs related to the patient mix include the number of MS patients and their distribution across the three most used DMTs in the UK (ocrelizumab, natalizumab, alemtuzumab), as well as the number of non-MS patients.

### 2.3.2 Treatment-Specific Parameters

Model inputs related to treatment include frequency of administration, infusion duration and frequency of IRRs. To populate the model, information on the posology of each

**Fig. 1** Conceptual structure of the process flow model. *IRR* infusion-related reaction
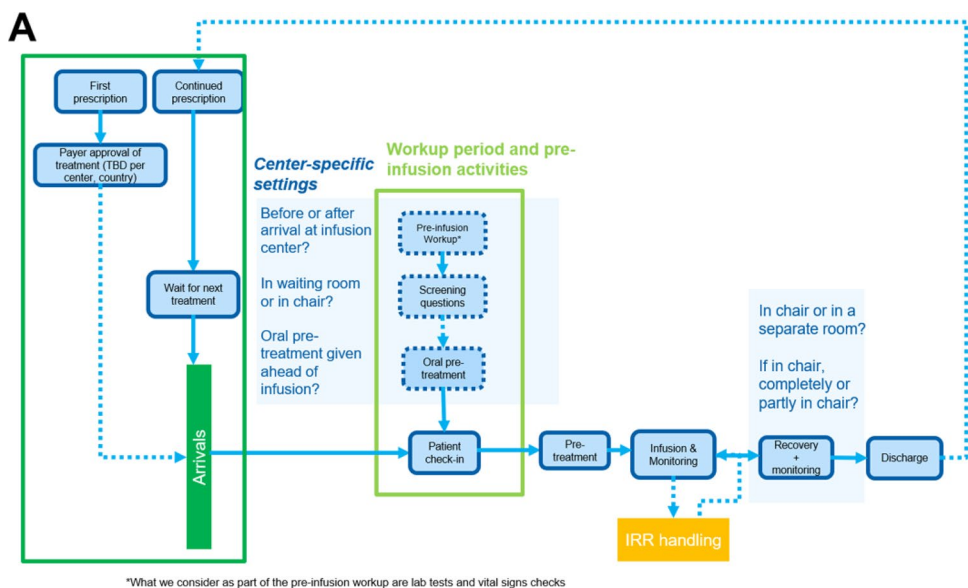
of the MS DMTs was obtained from the respective SmPCs (Table 2). Additionally, information on the minimum and maximum duration of the infusion was calculated from the recommended administration rates and the dose. For non-MS DMTs, a generalised infusion duration for the whole non-MS DMT treatment class was created, based on the duration of infusion for the three most used non-MS infusions in the UK (intravenous immunoglobulin, infliximab, and rituximab) and their respective SmPCs. The treatment-specific assumed frequency of IRRs was based on the SmPC, literature (including results of clinical trials for the DMTs)

or on a clinical insight, if there were no data available. These assumptions are detailed in ESM Table 2. First-infusion IRR rate is assumed to be higher than succeeding infusions, except for natalizumab.

The timing of infusion appointment was scheduled using triangular distribution, while the period between appointments was fixed as per the drug posology. The model is executed on a first-come, first-served scheduling; however, prioritisation was applied for alemtuzumab patients who needed 5 consecutive days of treatment, i.e., if they started
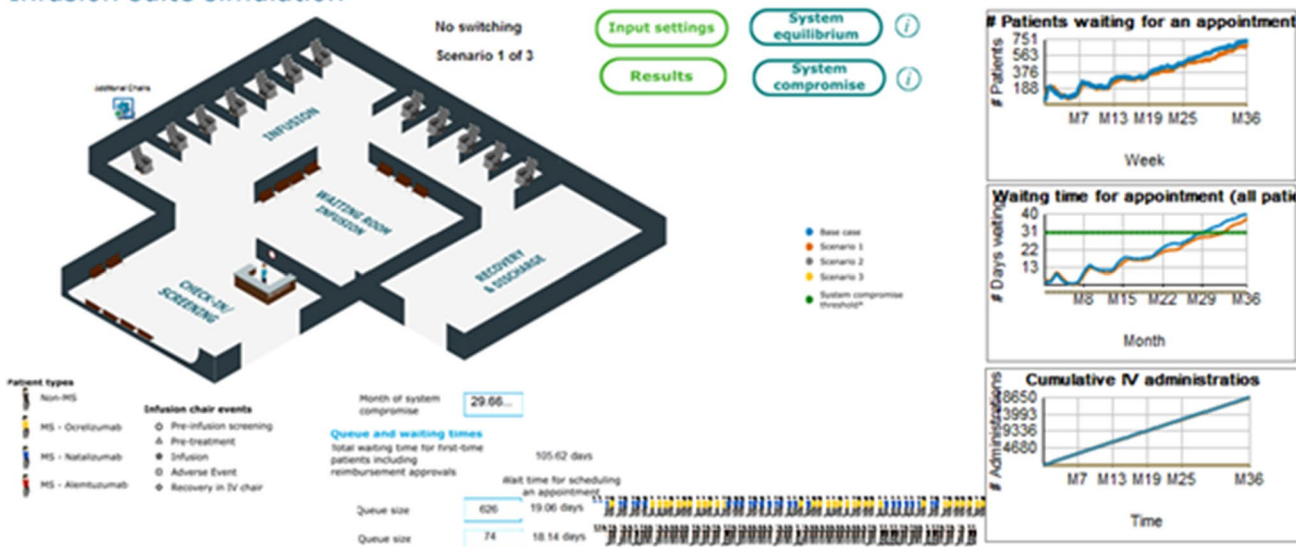


**Fig. 2** Current user interface. Input settings include *Centre settings* (chair and bed capacity, treatment pathway, number of patients, scheduling, did not attend rate, number of staff, staffing costs) and *Treatment settings* (posology, IRR rates, medication and IRR costs, payer approval time). *IRR* infusion-related reaction, *IV* intravenous

**Table 2** Posology and expected duration of infusion for MS and non-MS DMTs

| DMT | Duration of infusion (minimum–maximum) [h] | Total dose administered [mg/day] |
|---|---|---|
| *Ocrelizumab* | | |
| Initial dose (two infusions): infusion 1 | 2.5[a]–4 | 300 |
| Initial dose (two infusions): infusion 2 | 2.5–4 | 300 |
| Subsequent doses (one infusion every 6 months)[a] | 3.5–5 | 600 |
| *Natalizumab* | | |
| Once every 4 weeks | 1–2 | 300 |
| *Alemtuzumab*[b] | | |
| Initial dose (five consecutive infusions) | 4–8 | 12 |
| Maintenance, year 1 (three consecutive infusions) | 4–8 | 12 |
| Maintenance, after year 1, if needed (three consecutive infusions) | 4–8 | 12 |
| *Generic non-MS DMT setting*[c] | | |
| Initial dose (one infusion) | 2–6 | Not specified |
| Succeeding doses (most common: eight subsequent visits within 1 year, with one dose per visit)[d] | 2–6 | Not specified |

*DMTs* disease-modifying therapies, *MS* multiple sclerosis

[a]The recent approval of a 2-h administration protocol for ocrelizumab can be covered as a simulation scenario, rather than coded as a default parameter

[b]For alemtuzumab, the maximum was also based on the assumption that the infusion cannot take more than 8 h

[c]Generic range for the most commonly used non-MS infusions as well as those studied in other time and motion studies that include oncology patients, such as in De Cock et al. [16] and Schwartzberg et al.

[d]For non-MS DMT, the minimum, most common and maximum number of yearly visits were 3, 9 and 12, respectively (one dose being used for each visit)

the treatment, they would be scheduled with priority the next day.

For each non-MS patient, the expected number of visits per year were sampled and time to next appointment was estimated by assuming that the time between these treatment visits remained constant.

### 2.3.3 Healthcare Resources and Costs

Resources included in the model are the number of infusion chairs operating during a defined number of hours per day in the infusion centre, and nursing staff. Infusion chairs are modelled as a constraint in the model. Daily centre opening times can be user-specified.

Staff resource parameters include the number of staff nurses available and the time they spend on pretreatment, infusion, IRR handling, recovery and monitoring, and the percentage of time spent on activities not directly relating to patient care. Rather than using staff nurses as a resource constraint, a total pool of nurse hours (e.g., per week) spent on patient care was calculated. This was deemed reasonable based on clinical expert advice and to ensure balance between model usability/simplicity and complexity/realism. Following depletion of the total pool of staff nurse hours available based on the number of nurses employed by the

centre, it was assumed that all remaining activity was taken over by agency nurses charging a different rate from staff nurses. Time spent by pharmacists and neurologists was omitted in the model owing to the largely limited amount of time they spend in the infusion process, as compared with nurses. Other than labour, costs in the model include medication (DMT, premedication, medication used for IRR resolution) and supply costs [23]. Cost inputs are listed in ESM Table 3. The costs were according to the 2019/2020 National Tariff, which included both providers' and National Health Services' costs.

### 2.3.4 Scheduling Considerations

In case of patients who did not attend their scheduled appointment, it is assumed that the infusion chair is blocked for the duration of the originally scheduled appointment and cannot be used by another patient. This was deemed reasonable by the clinical expert as it is not feasible to schedule another patient at short notice.

## 2.4 Model Outputs and Scenario Simulation

The outputs of ENTIMOS include six key performance indicators (KPIs) that reflect the efficiency of an infusion

**Table 3** Results derived from ENTIMOS

| KPI | Results presented under KPI | Description |
|---|---|---|
| Patient throughput | No. of IV administrations performed (per month)<br>Change in expected cumulative IV administrations with respect to base-case simulation | A positive value indicates that more IV administrations are performed in a given scenario compared with the base-case, whereas a negative value indicates that less IV administrations are performed compared with the base-case |
| Patient waiting time | Waiting time for appointment scheduling (no. of days)<br>Cumulative waiting times for appointment scheduling (no. of days per 10 patients)<br>Average waiting time from payer approval to scheduling of first infusion (no. of days)<br>Monthly average within-centre waiting times (no. of minutes)<br>Cumulative within-centre waiting times (no. of hours per 10 patients) | No. of days between the current and next infusion appointments<br>Only for patients receiving a given IV DMT for the first time<br>Refers to the waiting time that a patient has from arrival at the centre until being seated on an infusion chair |
| Patient queue size | All patients<br>MS patients only<br>Non-MS patients only<br>Queue size per MS DMT | No. of patients waiting for appointment at the end of the month |
| Resource utilisation (staff) | Monthly average agency nurse hours needed per 10 patients<br>Cumulative agency nurse hours needed per 10 patients | No. of hours for patient care that could not be covered by the bank of staff nurse hours |
| Chair utilisation | Scheduled chair utilisation<br>Actual chair utilisation<br>Opportunity loss of unused chair time | Percentage of clinic operating hours that a chair is booked<br>Percentage of scheduled chair utilisation that the chair is actually used<br>No. of 4-h infusions that could have been administered if chair utilisation was optimal |
| Costs | Drug costs, in the following categories:<br>  premedication<br>  DMT (MS and non-MS)<br>  concomitant medication<br>  medication used for IRR resolution<br>Cost of supplies (infusion set, including bags and tubes)<br>Labour costs<br>  staff nurse<br>  agency (bank) nurse<br>  surcharge for weekend/bank holidays<br>Infusion administration reimbursement (payer's cost, centre's revenue)<br>  Base fee/fee for the initial hour of infusion<br>Fee for succeeding hours | Cost results are presented broken down by treatment (ocrelizumab, natalizumab, alemtuzumab, and non-MS treatments) and by subsequent visits<br>The total costs are not summarised, given that the cost components represent different cost perspectives |

*DMT* disease-modifying therapy, *IRR* infusion-related reaction, *IV* intravenous, *KPI* key performance indicator, *MS* multiple sclerosis

centre's operations across different domains: patient throughput, patient waiting time, patient queue size, staff utilisation, chair utilisation, costs (Table 3).

### 2.4.1 Waiting Time and System Compromise

System compromise is defined as patients facing an average delay of ≥ 30 days before receiving their next due infusion (as per approved use in SmPC) due to increasing waiting times for appointments in an infusion centre. It was selected as the focal metric due to its clinical relevance and potentially direct detrimental impact on MS progression [9, 10]. A centre can still operate under system compromise; however, the prolonged treatment delays put patients at risk. Waiting time indicates the extent to which a centre can avoid severe implications of missed or delayed patient treatment. This metric also helps centres understand how to mitigate treatment delays.

### 2.4.2 Corrective Action to Reach System Equilibrium

System equilibrium is defined as a situation where the average waiting time for the next due infusion does not exceed 30 days, evaluated monthly. Annual marginal corrective actions are defined as those that are required to prevent system compromise, resulting in a system equilibrium over the entire simulation horizon. The annual cycle for corrective actions reflects yearly planning cycles at Charing Cross Hospital.
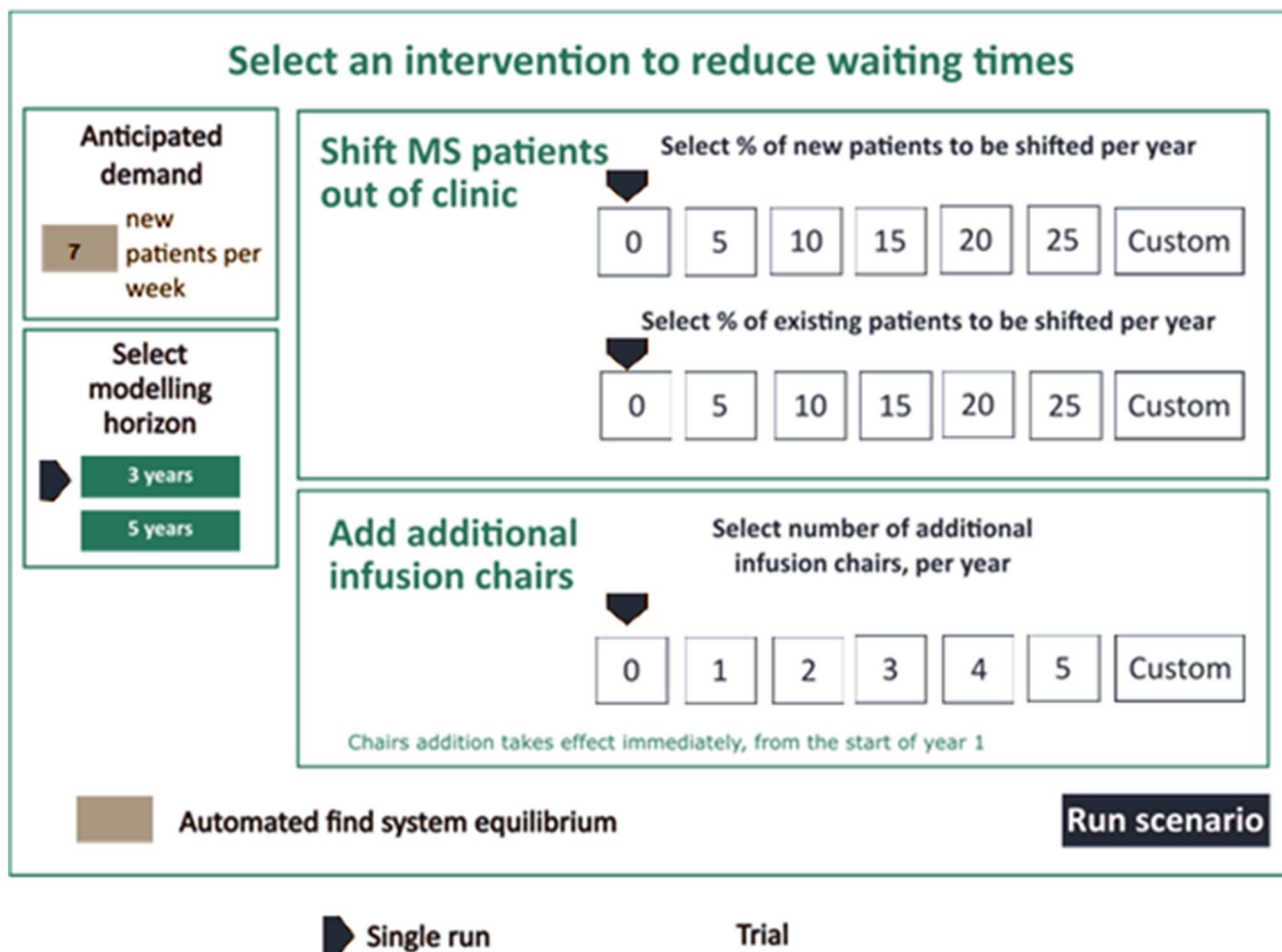
**Fig. 3** ENTIMOS user interface for facilitated scenario analysis—corrective actions needed to reduce waiting times and maintain system equilibrium over a selected time horizon. *MS* multiple sclerosis

Besides these automatically evaluated corrective actions, the model provides flexibility to define various scenarios that can be evaluated on a granular, monthly level through manual model runs.

The model allows for simulation of effects of three types of corrective action to reduce waiting times: (1) adding new infusion chairs, and (2) switching out new patients or (3) existing patients, by referring them to other clinics or offering them an alternative treatment not requiring infusion. New patients switched out are assumed not to enter the infusion suite. Existing patients who are switched out are removed from the system gradually over the duration of the entire year, proportionately to their distribution at day 1 (i.e., of each 100 patients who were shifted out, 64 were ocrelizumab patients and 36 were natalizumab patients). Since alemtuzumab was not used at Charing Cross Hospital at the time of the study, it is not included here.

The marginal annual corrective action is automatically determined by the model through a binary search algorithm

for patients switching, and stepwise increase for infusion chairs by an increment of one chair. User interface for manual testing of different corrective actions and automated search of marginal corrective actions is presented in Fig. 3.

### 2.4.3 Simulation Horizon

The current version of the model supports simulations up to 5 years. In this analysis, a 3-year horizon was chosen to reflect a typical planning horizon at an infusion centre. To build a realistic queue of patients being already in care at time 0, base-case simulations were run over a 24-week warm-up period before collecting the results. Twenty-four weeks was selected as the minimum warm-up period time, allowing all patients to show up in the system at least once before results are collected and removing seasonality effect (all patients with the same treatment being scheduled on the same day). Different durations of the warm-up period were tested, and warm-up periods longer than 24 weeks

**Table 4** Simulation results—marginal corrective actions to maintain system equilibrium over a 3-year horizon

| | Base-case | Marginal corrective action (automatically determined) | | |
| --- | --- | --- | --- | --- |
| | | Add one additional infusion chair (annually) | Shift out 24% of new patients (annually) | Shift out 7% of existing patients (annually) |
| Total no. of MS patients after corrective action[b] | 1952 | 1952 | 1690 | 1589 |
| Of whom were new | 1092 | 1092 | 830 | 1092 |
| Of whom were existing | 860 | 860 | 860 | 497 |
| No. of patients shifted out of the centre[b] | 0 | 0 | 262 | 363 |
| Total no. of IV administrations performed (number[a] and percentage change from base-case[b]) | 18,677 | 22,020 (+ 17.90%) | 18,784 (+ 0.58%) | 18,648 (− 0.15%) |
| Queue size at the end of simulation ($n$)[a] | 714 | 457 | 531 | 546 |
| Mean monthly chair utilisation (percentage of chair hours)[b] | 90.2 | 90.0 | 90.2 | 90.3 |
| Mean monthly nurse hours (hours[a] and percentage change from base-case[b]) | 1296 h | 1508 (+ 16.41%) | 1296 (0%) | 1297 (− 0.03%) |
| Labour costs (£[a] and percentage change from base case[b]) | £981,155 | £1,142,009 (+ 16.39%) | £970,189 (− 1.12%) | £971,976 (− 0.94%) |
| Of which were staff nurses | £589,231 | £585,785 (− 0.58%) | £584,296 (− 0.84%) | £585,869 (− 0.57%) |
| Of which were agency nurses | £391,924 | £556,224 (+ 41.92%) | £385,893 (− 1.54%) | £386,107 (− 1.48%) |

*IV* intravenous

[a]Direct model outputs

[b]Results derived based on model outputs

prolonged the computation time without changing the results substantially.

## 2.5 Model Verification and Validation

The verification and validation of ENTIMOS was performed in multiple steps. The process flow used by the model was validated for clinical accuracy and level of detail by two experts (Dr. Richard Nicholas and Dr. Praveen Thokala) via videoconferencing. To reduce the possibility of bias, the model code was verified by Dr. Thokala, an independent health economist who did not participate in its programming. Definitions of system compromise and model outputs were then validated by Dr. Nicholas, a clinical expert involved in the process.

## 3 Results

For demonstration, the model was parameterised with input parameters collected at the Charing Cross Hospital in March 2021. The Simul8 trial calculator recommended a trial of five simulation runs to obtain a point estimate and 95% confidence interval for the result metrics (Table 4). At that point of time, the infusion unit had 12 infusion chairs and operated 12 h a day, 5 days a week. The infusion appointments were booked starting at 8:00 am, and the longest possible time for a given infusion was blocked to prevent unnecessary in-clinic waiting for patients. Additionally, only three

natalizumab slots could be booked/chair/day. The did not attend (DNA) rate was 2%. The infusion centre employed 10 staff nurses and served 860 MS patients (552 ocrelizumab, 308 natalizumab), as well as 170 non-MS patients. The process flow for the administration of non-MS treatments was sufficiently similar to that of MS DMTs and was handled in the model using the same pathway. Based on the advice from a clinical expert (also co-author of this study), the future demand increase was assumed to be seven new MS patients per week, out of whom six (87%) were expected to receive ocrelizumab and one (13%) was expected to receive natalizumab. The number of non-MS patients was assumed to be constant.

### 3.1 Waiting Time and System Compromise

In a base-case scenario with the input parameters described above, the total number of MS patients in care was estimated to be 1952 (860 existing and 1092 new) and the cumulative number of intravenous administrations was estimated to be 18,677 over a 3-year simulation horizon (Table 4). Average monthly waiting times are presented in Fig. 4. The waiting time for an appointment (MS and non-MS) was estimated to be, on average, 8 days beyond clinical recommendation in year 1, 19 days in year 2, and 31 days in year 3 of the simulation (results not presented). The infusion centre ran at capacity from the beginning of the simulation and was predicted to reach system compromise (where delay in receiving due treatment is 30 days or longer) within 30 months.

**Fig. 4** Charing Cross Hospital scenario: waiting time for scheduling and infusion appointment with and without corrective actions
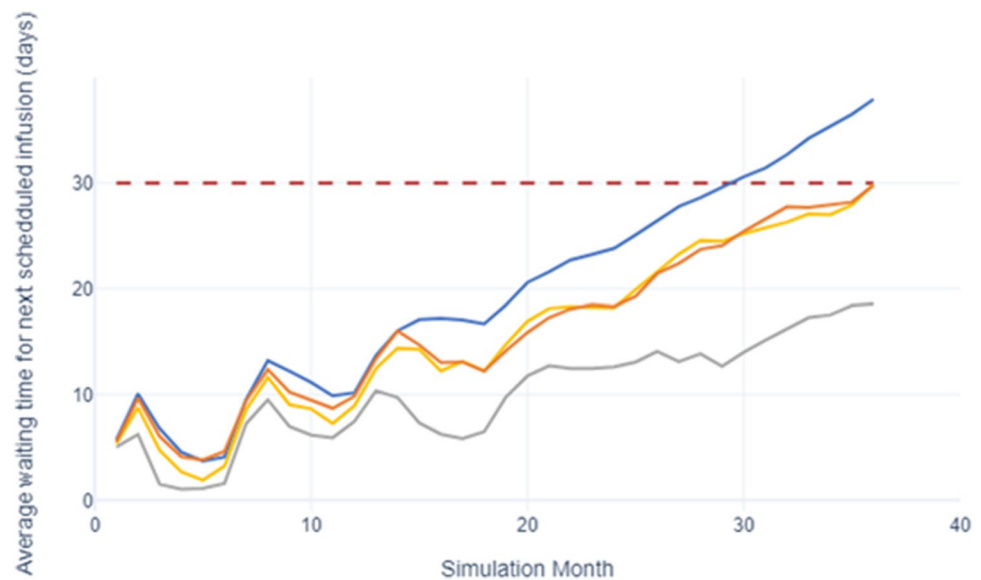


## 3.2 Corrective Actions to Prevent System Compromise

Marginal corrective actions identified by the model as able to maintain system equilibrium over 3 years, as well as selected KPIs for these scenarios, are presented in Table 4. One additional infusion chair per year was able to accommodate the anticipated demand without the need to shift any patient out of the centre during the simulation period. Alternatively, 7% of existing patients (total of 363, resulting in 1589 patients in care after 3 years of simulation) or 24% of new patients (total of 262, resulting in 1690 patients in care after 3 years of simulation) could be shifted out of the centre annually by referring them to other clinics or switching them to alternative non-intravenous treatments, maintaining system equilibrium.

Adding one additional chair per year increased the number of intravenous administrations to 22,020 (+18% from the base-case). In the switching scenarios, the number of intravenous administrations remained at the same level as in the base-case (±1%). The reported minimal differences (29 fewer infusions compared with base-case when switching out 7% of existing patients, compared with an additional 107 when switching out 24% of new patients) are due to the proportion of patients expected to receive ocrelizumab, which is higher among new patients (six of seven MS patients = approximately 86%) compared with existing patients (552 of 860 MS patients = approximately 64%). This assumption was based on the treatment undergone by patients at the Charring Cross Hospital during the study. The number of patients in the waiting queue and their breakdown by treatment type is illustrated on Fig. 5, showing that the proportion of ocrelizumab patients in the waiting line is also increasing with time. This is because ocrelizumab requires longer infusions than natalizumab, leading to these patients potentially waiting longer.

While queue size gradually increased over time in all scenarios (Fig. 5), adding one additional chair per year resulted in the shortest patient queue compared with other considered scenarios (Table 4). However, this led to an increase in the number of nurse hours needed by + 16.41%, corresponding to a + 16.39% increase in labour costs compared with the base-case scenario (from £981,155 to £1,142,009). The increase in labour costs is driven by the need to contract additional nurse time from a nurse bank (+ 41.92% in the agency nurse cost compared with the base-case scenario). Conversely, switching patients out of the infusion centre maintained the number of monthly nurse hours needed and associated costs at a similar level compared with the base-case scenario. Complete cost results are included in ESM 4.

Mean monthly chair utilisation was consistently high (> 90% of chair hours) across all scenarios due to the above-mentioned fact that in all scenarios, the infusion centre operated at capacity. The unused 10% of chair-hours capacity indicates that efficiencies can be achieved at the infusion centre, for example through improving the scheduling methodology.

## 4 Discussion

This study represents the first DES model estimating the impact of healthcare system constraints on the infusion treatment pathway for MS. Simulation of resource constraints serves as an insightful tool in healthcare systems [18, 24–30], but to our knowledge have not been used in MS. There is a rise in demand for infusions that puts pressure on treatment centres [11, 14]. In this study, we demonstrate how
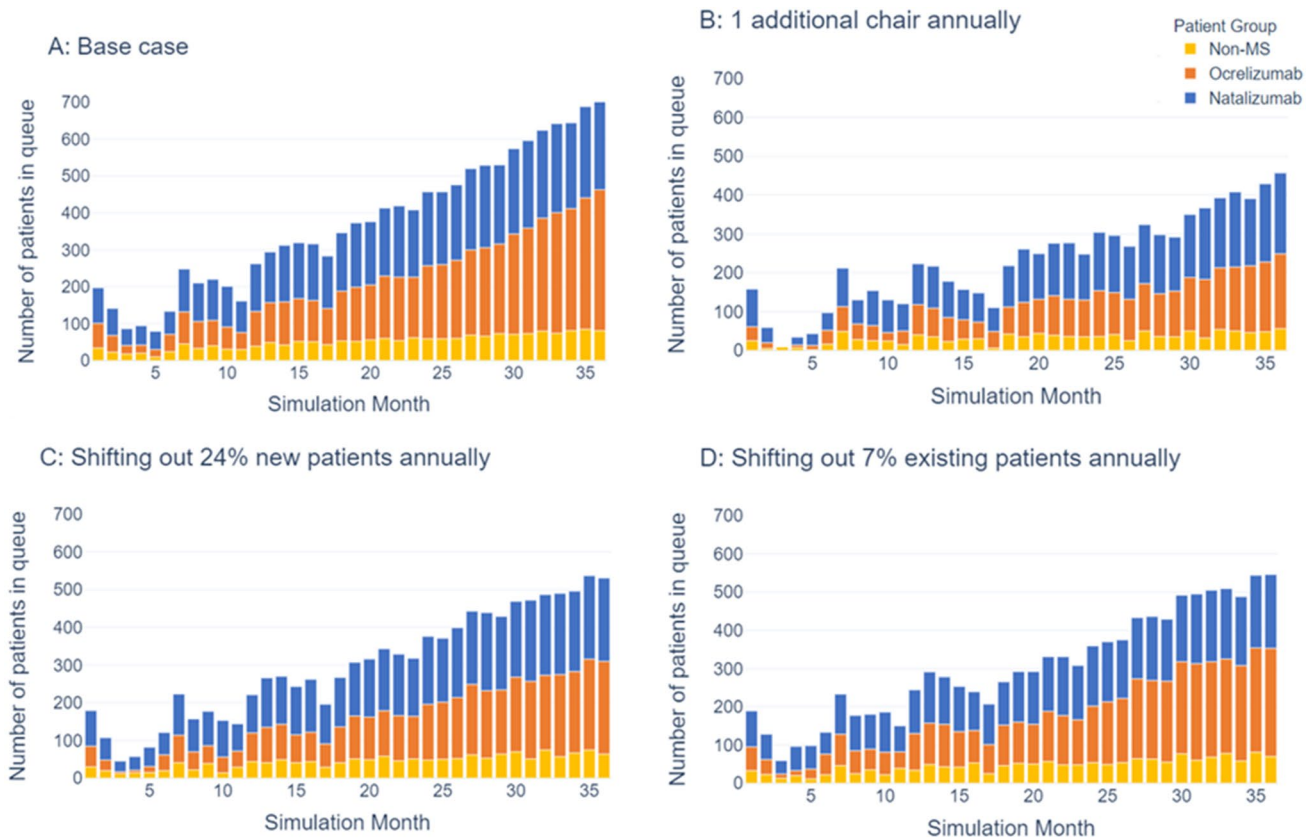
**Fig. 5** Queue size over the simulation period: number of patients waiting for infusion, broken down by treatment, with and without corrective action. **a** Queue under the base-case scenario without intervention. **b–d** Queue under scenarios where marginal corrective actions needed to assure system equilibrium were automatically defined by the model. *MS* multiple sclerosis

ENTIMOS, a simulation model, could be used to forecast impending changes and optimise resources to benefit infusion centre administrators, and ultimately the patients. By using a study case, the aim of this paper was to showcase both the functionality of our DES model and its adaptability to other settings.

For centre administrators, a simulation model can provide information needed to anticipate and proactively manage resource constraints and anticipate crises. A modelling approach may also assist patients in receiving more timely treatment with potential for better outcomes and improved experience. This is especially relevant for infusion centres where resources are shared with patients from other therapeutic areas (e.g., oncology, rheumatoid arthritis). Infusion centre chair resources were significantly depleted during peaks of the COVID-19 pandemic, causing prolonged waiting times and detrimental impacts on patient outcomes.

This DES model has three limitations. The estimation of staff resources and associated costs over simulated time horizons were not modelled as a constraint. Instead, it was assumed that agency nurses would be able to undertake any excess activity once staff nurse resources were depleted. This

was based on the experience at Charing Cross where no infusion appointment was cancelled due to nurse unavailability at the time the model was developed. However, a new version of the model is currently under development with nurse constraint as an optional function to increase applicability of the model to other infusion centres where staff availability might be the factor responsible for prolonged waiting time.

The current model assumptions do not allow the estimation of pharmacist and neurologist time and costs. While these may be relatively less significant compared with nurse costs, they may have some impact on marginal resource changes over a long period. Finally, in this chronic disease setting, all patients are assumed to remain in the system. Although the model contains a functionality to specify the percentage of patients outflowing each year (e.g. due to death), this option was disabled in the current simulation. The rationale behind this decision was the consideration that the impact of patient outflow on treatment demand and patient waiting times would be insignificant over a 3- to 5-year horizon in this chronic disease setting. Therapy discontinuation is not anticipated to occur with sufficient frequency to have a substantive impact on results. Switching

patients to treatments not requiring infusions is specifically captured through scenario analysis where users can explore consequences of switching new and existing patients. Switching across different intravenous DMTs is not modelled explicitly, but changes in treatment patterns can be reflected in the model by specifying the mix of newly diagnosed patients in terms of treatments they receive.

The ENTIMOS model was designed to inform strategic decisions for long-term planning and is currently not suitable for short-term (i.e., weekly or monthly) scheduling decisions. To model these scheduling decisions, exact data on the types of patients and the staff skill mix and rotations would be needed [31, 32]. Long-term simulation predictions are not precise estimates because patient numbers may be different to the parameterised inputs. ENTIMOS can forecast the outputs for strategic planning for any specific local setting.

The design choices in the process flow were based on data collected from a sample of eight diverse international sites in the UK and US that are assumed to be representative of all types of intravenous infusion sites. The model has the flexibility to represent different infusion centres by amending the infusion pathways and input parameters based on the variability in pathways and settings observed in these eight sites. Nevertheless, it is possible that unique patient flows of some infusion centres cannot be adequately represented using ENTIMOS. The modelling approach offers flexibility in being able to estimate the potential impact of different scenarios, including unanticipated events such as COVID-19, and other system changes resulting in the process flow being different from the one currently used in this DES model.

## 5 Conclusions

Utilising a resource planning tool allows long-term capacity planning with an outlook of increased productivity, quality of service, and efficiency. A decision analytics approach using a model such as ENTIMOS could be utilised to support planning decisions at Charing Cross Hospital and other infusion clinics on an annual basis. The model described here can be adapted for use in different settings by customising the process flow and input parameters related to the number and mix of patients, treatments and centre resources. Infusion suites could benefit from tools outlining how to make the most efficient use of resources, especially now when constrained healthcare systems strive to recover from the COVID-19 pandemic. This type of approach puts patients' interests at the centre of resource allocation decisions and supports clinics by identifying the necessary corrective measures to assure continuity of care.

## Declarations

**Author contributions** IB, CL, NA, and PD conceptualised the study. KL, PT, RB, CL, NA, PD, ES, and ZA performed research methodologies. KL, PT, RN, PD, ES, ZA, RB, and NA were involved in formal analysis and investigation. ES and ZA prepared the first draft. All authors reviewed and approved the manuscript. Funding was acquired by NA and supervision was provided by RB and NA.

**Conflict of interest** Kristyna Lacinova is a full-time employee of Simul8 Corporation Ltd. Praveen Thokala is the director of PT Health Economics Ltd and advised Novartis on this study on a consultancy basis. He has also performed paid consultancy in the past with IQVIA, RTI-HS, Roche, Pfizer, Daiichi Sankyo, Abbvie, Novo Nordisk and Novartis. Richard Nicholas is a paid employee of Imperial College Healthcare NHS Trust, London, UK, and has acted as a paid consultant in the past for Biogen, Roche, Teva, Merck, and Novartis. He has also received research funds from and worked on clinical trials run by Biogen and Novartis. Pamela Dobay, Erik Scalfaro and Zuzanna Angehrn are full-time employees of IQVIA AG, Basel, which received funding from Novartis Pharma AG to design, conduct and interpret the reported analyses. Roisin Brennan is a full-time employee of Novartis Global Services Centre. Ibolya Boer, Carol Lines, and Nicholas Adlard are full-time employees of Novartis Pharma AG.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** Not applicable since the model did not use patient-level data. Data were sourced from publicly available literature and assumptions based on clinical experience of one of the co-authors.

**Code availability** Models were developed using Simul8 proprietary software; extracts from the model codes were available to the reviewers upon request. The feasibility of making the model publicly available is currently being evaluated.

**Ethics approval** Not applicable since patient-level data have not been used in this study.

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