Discrete event simulation and treatment sequencing cost-effectiveness model in second line highly active relapse remitting multiple sclerosis for a NICE Multiple Technology Appraisal

EE336

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Objectives

The University of Bristol (UoB) Technology Appraisal Group (TAG) undertook a Multiple Technology Assessment (MTA) for the National Institute for Health and Care Excellence (NICE):

- Assessing the cost-effectiveness (CE) of natalizumab originator and biosimilar at 2nd line for Highly Active Relapsing Remitting Multiple Sclerosis (HARRMS).
- Addressing shortcomings of prior Excel-based cohort Markov models by flexibly modeling natural history, treatment switching, and up-to-date severity-dependent mortality.
- Building a Discrete Event Simulation (DES) model, implemented in the R language[1] and run on the computational facilities of the Advanced Computing Research Centre at UoB.
- Assess decision uncertainty with probabilistic analyses and Value of Information (VOI).

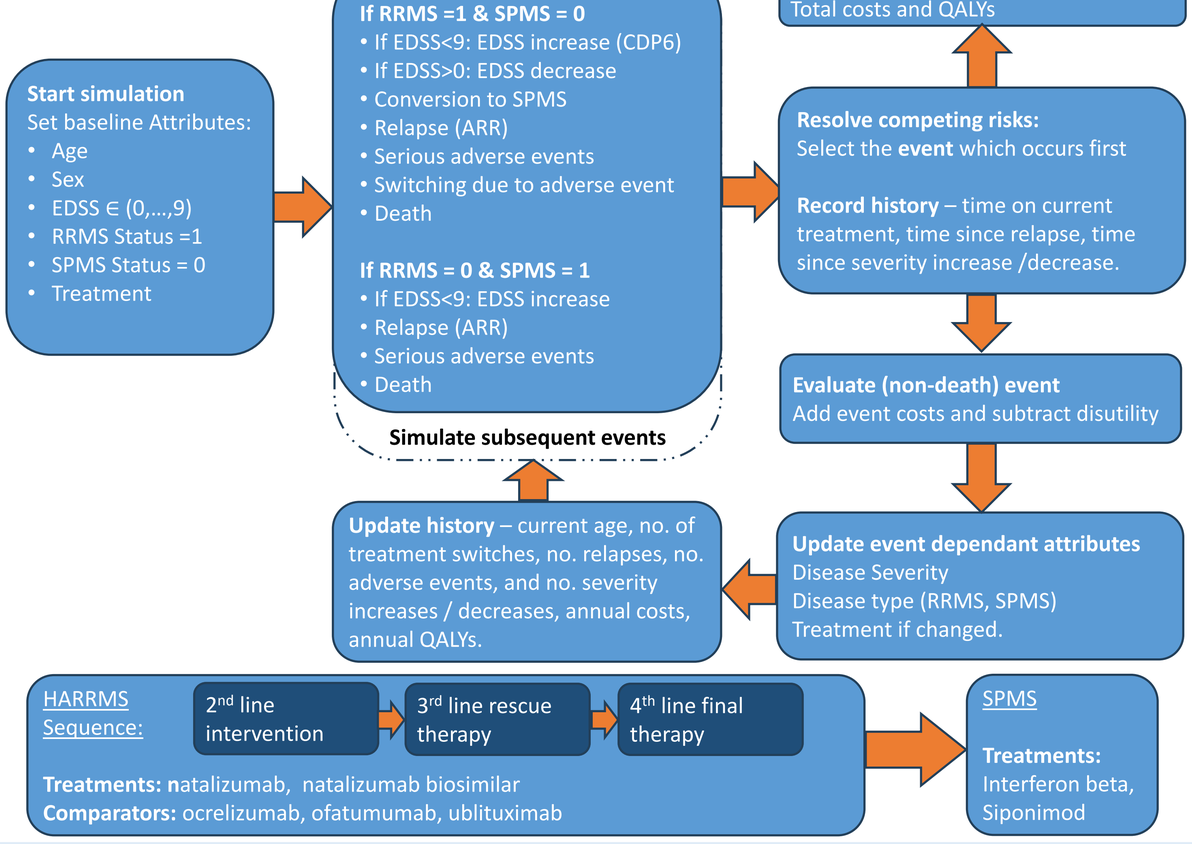
Background

- HARRMS patients have unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT).
- Eligible DMTs were natalizumab (Tysabri®, Biogen) and natalizumab biosimilar (Tyruko®, Sandoz), ocrelizumab (Ocrevus®, Roche), ofatumumab (Kesimpta®, Novartis) and ublituximab (BRIUMVI®, TG Therapeutics).
- The following shortcomings of the previous Markov models in RRMS were identified in a review of CE models used in UK decision making by NICE for Technology Appraisals:
  - Unrealistic representation of treatment sequencing, not allowing patients to switch on to alternative treatments.
  - Limited accuracy in modelling natural history, reflected in unrealistic disability progression / conversion to Secondary Progressive Multiple Sclerosis (SPMS).
  - Outdated modelling of the MS specific risk of death stratified by Expanded Disability and Severity Scale (EDSS).

Methods

An individual patient level DES with up to three lines of treatment was developed and programmed in R using the DESCEM package.[2] The DES overcomes limitations of cohort Markov models by conditioning events on patient attributes and history in continuous time.

Figure 1 Model Diagram



Model Inputs

UOB TAG undertook a systematic review of CE studies for interventions in HARRMS after at least one DMT that included n=7 evaluations. An overview of model inputs is given in Table 1:

Table 1 – model inputs

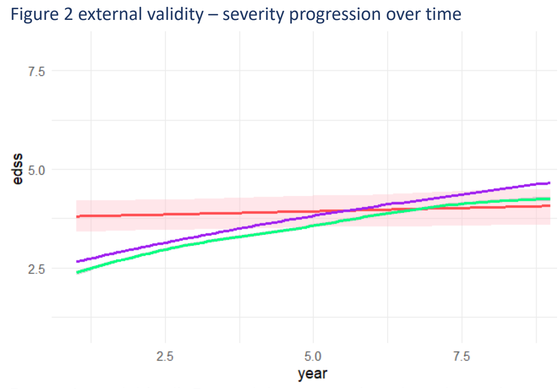
Parameters	Sources of data and methods
Base-line events: ARR, EDSS increase / decrease, conversion to SPMS	RWE from the MSR on (n=1261) RRMS and HARRMS patients.[3] Exponential models fit to interval censored data.
Treatment Effects: CDP-6 months, ARR, AE, AEltD	Bayesian NMA of outcomes modelled on the log ratio scale by assuming normality.[4] Implemented in R, multinma package.[5]
Treatment Sequences	RWE from the MSR, the proportion of patients on subsequent treatment at later lines.
MS-Specific Mortality	The average EDSS-specific SMRs followed GRPD data,[6] and the differences between EDSS categories matched RWE from the SWMSR.[7]
Costs & HRQoL stratified by EDSS [8,9]	Treatment costs are list prices from the BNF, and resources use costs are from the NHS national cost collection 2023/2024.[10] Annual treatment visits, monitoring visits, and proportions of patients re-treated were informed by expert clinical opinion. Costs and HRQoL due to AEs were calculated as a weighted average of those reported for natalizumab.[11]

***AE**: Adverse Events, **AEltD**: Adverse Events leading to Discontinuation , **ARR**: Annual Relapse Rate, **BNF**: British National Formulary, **CDP**: Confirmed Disability Progression, **EDSS**: Expanded Disability and Severity Scale, **GPRD**: UK General Practice Research Database, **HRQoL**: Health-related Quality of Life, **NMA**: Network Meta-Analysis , **MS**: Multiple Sclerosis, **MSR**: UK MS Register, **RWE**: Real World Evidence, **SWMSR**: Southeast Wales MS Registry, **SMR**: Standardised Mortality Ratio, **SPMS**: Secondary Progressive Multiple Sclerosis.*

Validation

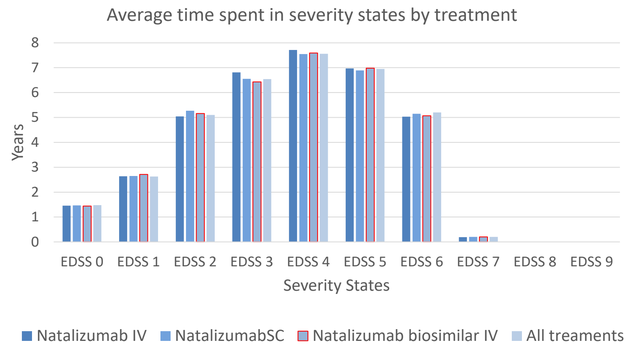
- Model code was independently verified by Javier Sanchez Alvarez at Evidera.
- Validity of model outputs are consistent with clinical experience of patients treated with modern DMTs.
- External validation for the rate of progression on severity against long-term data from an older data source[12] (figure 2) shows stable rate of severity progression reflective of current clinical practice.
- Face validity of time spent in EDSS states (figure 3) shows severity stable up to EDSS 6, does not exceed EDSS 7, and was not influenced by treatment.

Figure 2 external validity – severity progression over time



Economic model (red) External data source (purple and green)

Figure 3 Face validity – distribution across severity states



Results

- The results converge with only 1000 samples x 100 patients. For decision-making, UoB TAG ran 1000 samples x 1000 patients on the UoB high-performance computing facility.
- Public prices results are summarized using incremental net monetary benefit (INMB) at £20,000/QALY 95% Credible Intervals (CrI).
- Natalizumab originator subcutaneous (SC) had highest INMB £26,128 (£11,466, £42,177) In comparison to natalizumab originator (IV).

Table 2 – public prices model results (1000 samples x 1000 patients)

Treatments	Net benefit at £20,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)
Natalizumab-IV	-£161,172 (-£213,811, -£118,991)	-
Natalizumab-SC	-£135,043 (-£190,627, -£94,170)	£26,128 (£11,466, £42,177)
Natalizumab biosimilar-IV	-£150,142 (-£206,955, -£108,734)	£11,030 (-£4,983, £27,367)
Ublituximab	-£199,298 (-£253,612, -£159,738)	-£38,126 (-£51,334, -£25,016)
Ofatumumab	-£201,346 (-£248,012, -£163,999)	-£40,174 (-£56,717, -£24,325)
Ocrelizumab	-£217,424 (-£263,540, -£180,789)	-£56,252 (-£76,794, -£37,831)

- Natalizumab-SC has the highest probability of being cost effective as shown in the CE Acceptability Curve (CEAC), but with very high uncertainty as shown in the CE Plane (CEP).

Figure 2 – Cost Effectiveness Acceptability Curve (public prices, 1000 samples x 1000 patients)

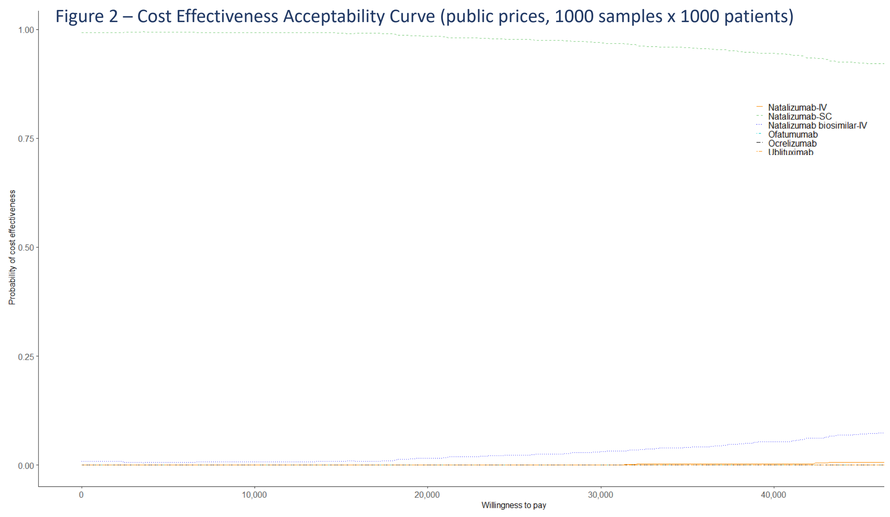
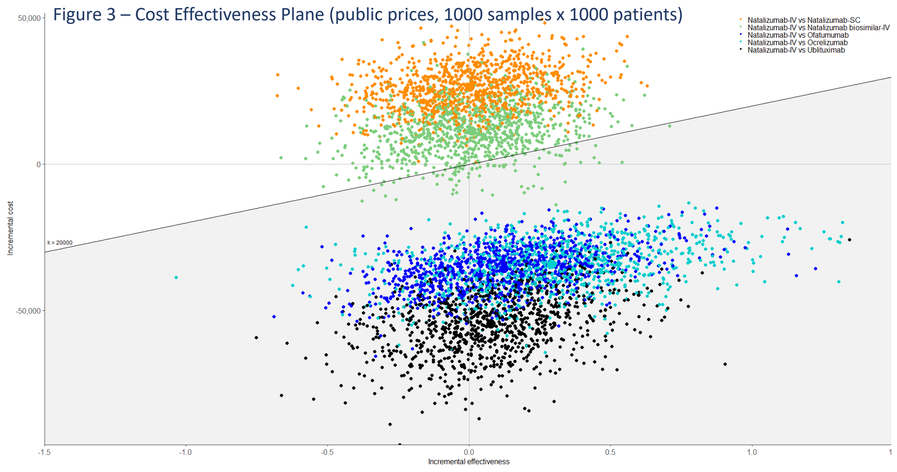


Figure 3 – Cost Effectiveness Plane (public prices, 1000 samples x 1000 patients)



- VOI indicated relative treatment effects on ARR, CDP6 and safety to be the greatest source of decision uncertainty.
- VOI also indicated baseline event rates, costs and HRQoL to have high uncertainty and be important factors in decision making.

Conclusion

- This was the first NICE MTA to use a DES model built in R.
- Predictions were better aligned with RWE and clinical opinion than previous Markov models in MS. This model was judged suitable for decision making by the NICE committee.
- The public prices results indicate a high degree of uncertainty.
- DMTs: ofatumumab, ocrelizumab and ublituximab are cost saving, but the potential for greater benefit was uncertain.
- The model will be updated to use the WARDEN package[13] and made available on GitHub.

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References

1. R. Core Team. R: A Language and Environment for Statistical Computing.2019.
2. Aponte Ribero V, Sanchez Alvarez J (2022). descem: *Discrete Event Simulation for Cost-Effectiveness Modelling*. R package version 0.1.2.
3. UK MS Register, Swansea University Medical School, URL: https://ukmsregister.org/.
4. Dias S, Welton NJ, Sutton AJ, et al. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials*.2016.
5. David M. Phillippo. *multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data*.2024.
6. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. Journal of Neurology 2014;261(8): 1508-1517.
7. Harding, Katharine et al. A contemporary study of mortality in the multiple sclerosis population of south east Wales. Multiple Sclerosis and Related Disorders, Volume 25, 186 – 191.
8. Tyas D, Kerrigan J, Russell N, Nixon R. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? *Value in Health* 2007;10(5): 386-389.
9. Kobelt G, Berg J, Lindgren P, et al Costs and quality of life of patients with multiple sclerosis in Europe. *Journal of Neurology, Neurosurgery & Psychiatry* 2006;77:918-926.
10. NHS England. *2023/24 National Cost Collection Data Publication*.2024. URL: https://www.england.nhs.uk/publication/2023-24-national-cost-collection-data-publication/.
11. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. The NEJM 2006;354(9): 899-910.
12. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M, *et al.* UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ Open* 2014;4(1): e004073.
13. Sanchez Alvarez J (2025). WARDEN: Workflows for Health Technology Assessments in R using Discrete EveNts. R package version 2.0.0, https://jsanchezalv.github.io/WARDEN/.