# The cost effectiveness of ocrelizumab for treatment of primary progressive multiple sclerosis in Aotearoa New Zealand, from societal and healthcare perspectives

## Report to Multiple Sclerosis New Zealand

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KEY POINTS FOR DECISION-MAKERS

1. Ocrelizumab (OCR) is the only disease modifying therapy currently available to treat primary progressive multiple sclerosis. It was publicly funded for this indication in New Zealand (NZ) in 2023. The list price is $37,384 per annum.
2. The modelled time to wheelchair-dependency or death ranges from 7.0 to 17.0 years depending on the disability level (EDSS) at diagnosis. OCR delays this by 4.0 to 6.0 years.
3. Treatment is more cost effective when it is initiated earlier in the course of disease and/or at younger ages.
4. Based on Treasury criteria, NZ could be justified in paying up to $NZ22,057 ($US13,779) per person per annum for treatment of PPMS with OCR, from a societal perspective, or $NZ4,673 ($US2,929) from a healthcare perspective (2022 NZ dollars, August 2023 exchange rate). The difference is due to inclusion of non-medical and indirect costs, particularly lost wages and productivity.
5. Treatment with OCR is cost neutral at 59% of list price from a societal perspective or 12.4% of list price from a healthcare perspective.
6. This study illustrates the importance of taking all relevant costs into account when evaluating new pharmaceuticals for chronic illnesses that require significant resources outside of usual healthcare budgets.

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# GLOSSARY

| | |
|---|---|
| ADL | Activities of Daily Living |
| AMSLS | Australian Multiple Sclerosis Longitudinal Study |
| AUD | Australian dollar |
| AQoL-8D | An Australian multi-attribute utility instrument for measuring HRQoL |
| BSC | Best supportive care |
| CBA | Cost-benefit analysis |
| CBAx | A cost-benefit analysis toolkit developed by the New Zealand Treasury |
| CDP | Confirmed disability progression |
| CEA | Cost effectiveness analysis (relationship between cost and effectiveness of intervention) |
| CUA | Cost utility analysis (CEA incorporating quality of life as QALYs) |
| DMT | Disease modifying therapy |
| EDSS | Kurtzke Expanded Disability Status Scale |
| EQ-5D | [a standardised 5-domain measure of health-related quality of life] |
| GBP | UK pounds currency |
| GDP | Gross Domestic Product |
| HR | Hazard ratio (the risk of disease progression while on therapy compared to no therapy) |
| HRQoL | Health-related quality of life |
| HSU | Health state utility (a number between zero and one representing HRQoL) |
| ICER | Incremental Cost Effectiveness Ratio (the ratio of incremental costs to incremental benefits of therapy in specified units) |
| ICUR | Incremental Cost Utility Ratio (the ratio of incremental costs to incremental benefits in QALYs)* |
| ITT | Intention to treat (the most conservative form of analysis of a clinical trial) |
| MRI | Magnetic Resonance Imaging |
| MS | Multiple Sclerosis |
| MSMM | Multistate Markov model |
| NICE | UK National Institute for Health and Care Excellence |
| NMB | Net monetary benefit |
| NPV | Net Present Value (the value of future costs or health benefits at today's prices) |
| NZ | Aotearoa New Zealand |
| NZD | NZ dollar |

| | |
|---|---|
| ORATORIO | Acronym for the pivotal clinical trial of ocrelizumab |
| PERT | A type of distribution, a minimum value, a maximum value, and a most likely value |
| PFPA | Pharmac's 'Prescription for Pharmacoeconomic analysis' version 2.2 |
| PPMS | Primary Progressive Multiple Sclerosis |
| PPP | Purchasing Power Parity [used to compare purchasing power across countries] |
| PPPA | Per Patient Per Annum |
| PRMS | Progressive Relapsing Multiple Sclerosis |
| PSA | Probabilistic Sensitivity Analysis |
| QALY | Quality Adjusted Life Year |
| RRMS | Relapsing Remitting Multiple Sclerosis |
| SMR | Standardised Mortality Ratio (ratio of disease-related mortality to population mortality) |
| SPMS | Secondary Progressive Multiple Sclerosis |
| TAR | Technical Assessment Report (by Pharmac) |

*ICUR is a subset of ICER. These terms are used interchangeably in this report

# EXECUTIVE SUMMARY

Multiple sclerosis (MS) is a progressive, degenerative, autoimmune neuronal disease. This study compares the impact of a societal versus a healthcare perspective on the cost effectiveness of treatment of primary progressive MS (PPMS) with ocrelizumab (OCR) versus best supportive care (BSC) and it estimates the impact of OCR on the time to wheelchair dependence/death.

The analysis utilises a lifetime Markov model based on 10 Expanded Disability Status Scale (EDSS) states, plus death. It has 2 structurally identical arms, with forward transition probabilities in the treatment arm multiplied by the 12-week disability progression hazard ratio in the clinical trial ORATORIO. Direct and indirect costs (in 2022 NZD) were estimated from the Australian MS longitudinal study. Future costs and benefits were discounted at 3.5% per annum. The model is calibrated to NZ mortality for PPMS, and therapy continues until EDSS6.

For a cohort 40 years of age starting at the ORATORIO distribution of EDSS, the median time from diagnosis to wheelchair dependence/death is 12 years for BSC and 17.5 years for OCR. OCR delays the median time to wheelchair dependence/death by 4 to 6 years, depending on the EDSS at initiation of therapy. Therapy is more cost-effective when it commences at younger ages and at earlier disability states. At 50% of the list price ($NZ37,384 per patient per annum) the incremental cost-effectiveness ratio (ICER) is $NZ98,490 per QALY ($US61,682) from a societal perspective or $NZ139,986 ($US87,671) from a healthcare perspective.

From a societal perspective the ICER is equal to a threshold suggested by NZ Treasury ($NZ120,200) when OCR costs 59% of the list price ($NZ22,057 per person per year) or a healthcare threshold ($NZ43,313) when it costs 12.4% of the list price ($NZ4,673 per person per year). Alternatively, an acquisition cost of 39.6% of list price ($NZ14,804) could be justified if the criterion of one GDP per capita ($NZ71,183) is used as a funding threshold. These results are sensitive to the cost of illness from a societal perspective but not from a healthcare perspective.

From both perspectives the cost effectiveness is sensitive to the acquisition cost and efficacy of OCR, the age and EDSS state when therapy begins, the cost and timing of a biosimilar pharmaceutical, possible waning of efficacy, inclusion or exclusion of carer quality of life and the discount rate. Extending therapy from EDSS6 to EDSS7 would have little impact on cost effectiveness. Treatment with OCR is equally cost effective at 50% of list price from a societal perspective or 10% of list price from a healthcare perspective. The net monetary benefit of OCR is positive at 10% of list price from both perspectives at WTP $40,000 or higher, but negative at 50% list price except at high societal WTP (>=$100,000).

In summary, treatment of PPMS with OCR is accompanied by a delay in wheelchair dependence/death which is greater with earlier diagnosis and treatment. OCR is considerably more cost-effective from a societal than a healthcare perspective, therefore a funding decision may depend critically upon the study perspective.

# 1. INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive, neurodegenerative autoimmune disease affecting the central nervous system, which is characterised by inflammation, demyelination and degeneration of neuronal axons. Mostly diagnosed in people from ages 20 to 50, the global prevalence of MS has been increasing [1], and MS is the commonest cause of progressive disability in the western world; thus identification of treatments that might significantly impact long-term disability outcomes is likely to reduce costs to payers and improve quality of life [2]. Primary progressive multiple sclerosis (PPMS) is typically characterised by progressive decline from onset, with occasional temporary plateaus or minor improvement [3]. The main presentation of PPMS is partial paralysis, especially of the lower limbs. Patients also experience impaired upper limb function [4]. A NZ study reported that 272 of 459 participants (59%) with progressive onset MS were female, in contrast to 1856 of 2386 (78%) with relapsing onset MS [5].

Aotearoa New Zealand (NZ) is a high-risk country for MS, with an overall age and sex standardised prevalence of 73.1 per 100,000 population [6]. In 2021, an estimated 4,130 persons in NZ (population 5.3m) had MS (https://www.nzier.org.nz/publications). The incidence and prevalence of multiple sclerosis have a clear latitudinal gradient, with relatively high rates in te Wai Pounamu (the South Island of NZ) [7] and in Australia (being more prevalent in its southern-most states) [8]. A study of 1727 New Zealanders with MS reported that the mean age at diagnosis was slightly less than 40 years, with wide confidence intervals. [9] For 459 individuals with progressive onset MS, the median survival age at birth was 9 years lower than that of the general population, with more than double the overall mortality risk compared to the general population [5].

Long-term MS-related disability severity is typically characterized using the Kurtzke Expanded Disability Status Scale (EDSS), with 3 main disability milestones: EDSS4 (limited walking but without aid), EDSS6 (walking with unilateral aid) and EDSS7 (wheelchair dependent), with escalating costs. Caregivers of patients with MS have been reported to experience high levels of distress and reduced health related quality of life [10]. Annual costs per individual for an international cohort including NZ patients for mild, moderate, and severe disability of the person with MS were US$1,123, US$6,643, and US$15,855, respectively [11].

MS is costly to healthcare and to society, particularly as MS-related disability severity increases (https://www.msaustralia.org.au/wp-content/uploads/2023/02/health-economic-impact-of-multiple-sclerosis-in-australia-in-2021_final.pdf) hence slowing of disability severity is likely to reduce annual MS-related health payer and societal costs. Early intervention with high-efficacy disease-modifying therapies may represent the best opportunity to delay disability progression. Most individuals in younger age groups in NZ who have MS are likely to be employed and are likely to reduce their degree of employment as disability progresses, with a consequent loss of family income and tax income to the government [9].

Ocrelizumab (OCR), a recombinant humanised monoclonal antibody that selectively depletes CD20-expressing B cells, is the only disease-modifying treatment (DMT) shown to slow disability progression in individuals with PPMS [12-14]. The main evidence for the efficacy of OCR administered to patients with PPMS comes from the ORATORIO clinical trial, which was an international, multi-centre, double-blind, randomised, placebo-controlled, phase 3 trial done at 182 study locations including New Zealand [13]. Patients were randomly assigned in a 2:1 ratio to receive 600 mg of OCR by intravenous infusion or matching placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred. ORATORIO included patients with MS who at screening were 18 to 55 years of age and had an EDSS state of 3.0 to 6.5. Pre-specified analyses on the intention-to-treat population showed that ocrelizumab reduced the risk of 12-week confirmed disability progression (i.e. the increase in EDSS that was present for at least 12 weeks) [disability progression hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.59–0.98] and had a similar effect on the risk of 24-week confirmed disability progression [13, 15].

OCR has been approved for use in patients with PPMS by the US Federal Drug Administration (https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-multiple-sclerosis) and recommended by the UK National Institute for Health and Care Excellence (NICE) ((https://www.nice.org.uk/guidance/TA585/chapter/1-Recommendations) and the European Medicines Agency (https://www.ema.europa.eu/en/medicines/human/EPAR/ocrevus). It was funded by New Zealand's Pharmaceutical Management Agency (Pharmac) in October 2023 while this study was in progress (https://schedule.pharmac.govt.nz/2024/06/01/SA2273.pdf). Treatment with OCR requires additional nurse and specialist time, and outpatient clinic chairs for infusions. Treatment is also likely to free up some health system resources by delaying the disability progression of PPMS – meaning that patients spend more time in less severe EDSS states that require fewer health system and other resources. This is also likely to improve employment outcomes [9].

Economic evaluations designed to inform public funding of pharmaceuticals and medical devices commonly include only direct medical costs and therefore take a healthcare perspective. Such studies could take the form of a cost-effectiveness analysis and/or a form of cost-benefit analysis (CBA) using net monetary benefit (NMB). However, CBA can take a societal perspective by including both healthcare and non-medical direct costs such as informal caregiver; specialised equipment; home/car modifications and patient transport, also indirect costs such as loss of actual or potential income [16, 17]. Pharmac limits its economic analyses to a healthcare perspective (https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/prescription-for-pharmacoeconomic-analysis-methods-for-cost-utility-analysis/) although many countries take a societal perspective [18]. Inclusion of non-medical and indirect costs and benefits is likely to affect the ranking of pharmaceuticals for funding under a capped budget (see the Discussion).

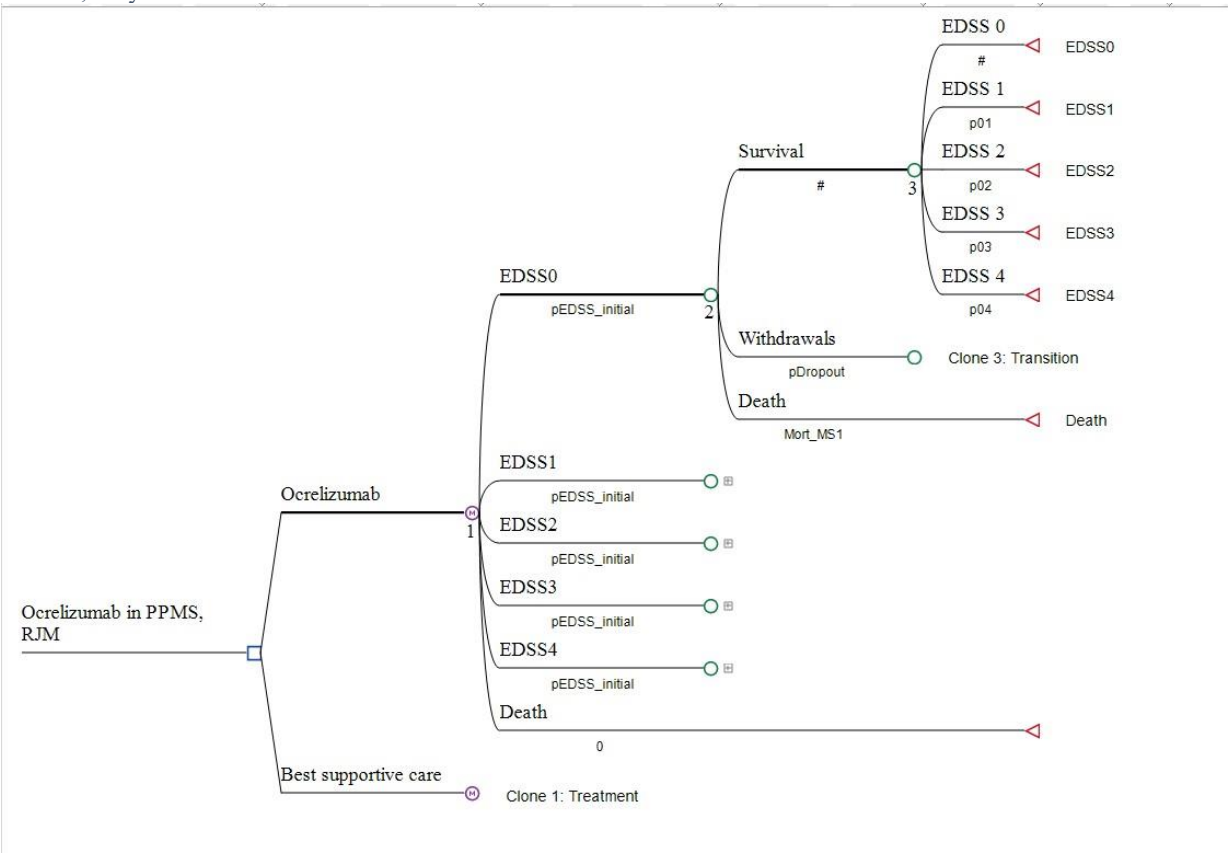
The primary purpose of this study was to determine the lifetime cost effectiveness of treatment of persons with PPMS with OCR versus best supportive care (BSC) from both healthcare and societal perspectives, using both cost-utility analysis and cost-benefit analysis. A secondary purpose was to estimate the impact of OCR on the time from commencement of treatment to wheelchair dependence. The plan was to develop a Markov model, populated from Australian, New Zealand and European sources, to establish the potential cost effectiveness of treatment of patients with PPMS with OCR.

# 2. METHODS

## 2.1 The economic model

The Markov model has 2 structurally identical arms, with forward transition probabilities in the treatment arm multiplied by the disability progression hazard ratio in the intention-to treat-analysis of the ORATORIO clinical trial (0.76) [13]. The model has 10 EDSS health states, plus death. It was developed using commercial software (TreeAge® Pro, 2024). The model considers a cohort of individuals living with PPMS who move progressively from diagnosis to EDSS9 or death from any cause **(Figure 1).** The start point of the model is the initiation of therapy with OCR or the equivalent time in the control arm, and the time horizon of the model is the lifetime of the cohort (terminating at age 95 years). A third arm (not shown) represents the general population (59% female [5]). The utility (quality of life) scale is anchored at zero for death and 1.0 for full health.

Figure 1. Schematic of the Markov model, showing progression between EDSS health states. For illustrative reasons, only 5 of 10 EDSS states are shown.




In the base case analysis, a simulated cohort of patients enters the model at 40 years of age. Each Markov cycle is 12 months. A standard half-cycle correction was applied, and all costs and benefits were discounted to net present value at 3.5% as required by Pharmac (https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/prescription-for-pharmacoeconomic-analysis-methods-for-cost-utility-analysis/) and also 5%, as suggested in guidance by NZ Treasury (https://www.treasury.govt.nz/information-and-services/state-sector-leadership/guidance/reporting-financial/discount-rates). Costs and benefits of treatment with OCR were applied to EDSS states 2.0 to 6.0 (see the Discussion). The model includes introduction of a biosimilar within 5 years of 2024 to correspond to patent life in Europe and the USA. We assumed that the biosimilar will be priced at 70% less than the rebated price of OCR while on patent (range 50% to 90%). This in accordance with

Pharmac's guidelines (https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/prescription-for-pharmacoeconomic-analysis-methods-for-cost-utility-analysis/). State transition probabilities represent the risk of an individual with PPMS progressing from a less severe to a more severe EDSS state, or (uncommonly) the reverse, within 12 months. The Markov model utilises annual state transition probabilities for PPMS patients diagnosed at less than 50 years of age to correspond to most NZ patients [9]. These were obtained from public UK NICE documents (https://www.nice.org.uk/guidance/ta585/evidence/). Specifically, table 46 was used, which is available on page 105 of the document "Appraisal consultation committee papers". The NICE review of a similar model of OCR in PPMS has been described elsewhere [15]. Fortunately, the probability of remaining in a health state is generally higher for no/mild disability (EDSS0 to EDSS3) than for higher health states, as reported elsewhere for a large Australian cohort, indicating longer dwell times in less severe disability states and more rapid progression of disability in more severe disability states [19].

## 2.2 Mortality

All forms of MS are progressive and potentially fatal. The standardised mortality ratio (SMR) is the number of observed deaths in the study population divided by the number of expected deaths in a given period. In NZ, the SMR for 459 individuals with progressive onset MS was reported as 2.2 (95% CI 2.0, 2.5) and life expectancy from birth was 9 years less than the sex-matched general population [20]. Mortality at each EDSS was estimated using the exponential function M=exp(-0.14xEDSS), which gives a life expectancy from birth 9 years less than the NZ population average for PPMS [5] (see the Supplement for details).

## 2.3 Quality of life

There are multiple sources for health state utilities (HSUs) for MS [13, 21-26] (https://www.msaustralia.org.au/wp-content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf). A study of 254 New Zealanders with all types of MS, using the EQ-5D-5L instrument, reported mean HSU for mild disability of 0.80, moderate disability 0.57 and severe disability of 0.14 [24]. Because the NZ study was relatively small and contained only three levels of disability, we utilised European HSUs [25] in our base case analysis because they were obtained from almost 17,000 participants in 16 countries.[25] For a group of 1577 participants in the Australian MS Longitudinal Study (AMSLS), HSU values by disability severity did not differ between relapsing remitting MS (RRMS) and PPMS cohorts [22]. Therefore we assumed that EDSS-specific HSU values determined across all phenotypes would apply to PPMS.

## 2.4 Costs

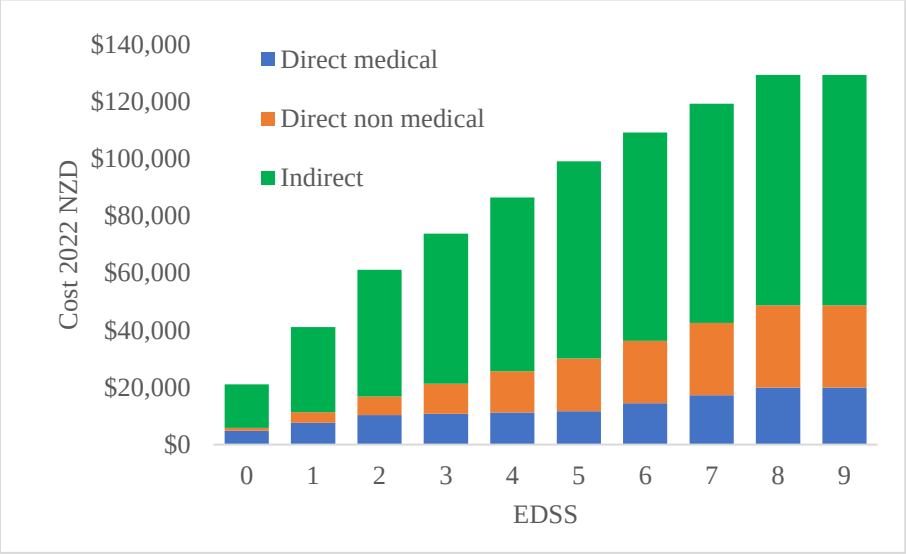
Our analyses utilised either (1) direct healthcare costs or (2) societal costs, which include direct healthcare costs plus direct non-medical costs such as carer support and house/car modifications plus lost productivity caused by absenteeism and/or presenteeism (reduced activity while at work) or unemployment. In a large European study across 16 countries, healthcare resource use was driven more by system organisation than by medical need [25]. Because detailed costs of MS by EDSS state are not available for NZ, we utilized costs based on resources in Australia, which we expect to be similar to those in NZ (https://www.msaustralia.org.au/wp-content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf; https://www.msaustralia.org.au/wp-content/uploads/2023/02/health-economic-impact-of-multiple-sclerosis-in-australia-in-2021_final.pdf). These were adjusted to NZD using purchasing power parities (PPP) and NZ consumer price indices (PPP in 2017 = 0.9685; NZ CPI in 2017 to 2022 = 1.1915). Fourteen percent of the Australian sample had PPMS.

The AMSLS utilised costs from 488 individuals in the Economic Impact Survey 2016 subset (https://www.msaustralia.org.au/wp-content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf). Costs were obtained from cost diaries which captured detailed information on various cost categories relating to MS. The report provides a breakdown of average annual costs in 2017 AUD by MS-related disability severity based on EDSS cut points (no EDSS=0, mild EDSS=1 to 3.5, moderate

EDSS = 4 to 6, severe EDSS = 6.5 to 9.5). Key cost categories comprise: direct (personal, community/government, nursing home and equivalent care, informal care) and indirect (lost wages and productivity including early retirement). In addition, there is a breakdown of total direct costs by key categories.

We converted Australian costs to 2022 NZD using purchasing power parity in 2017 inflated to 2022 values by the NZ consumer price index (see the Supplement for cost details). Because there are 9 EDSS states but only 4 levels of cost are available from the AMSLS, we used linear interpolation to provide intermediate costs, and we assumed conservatively that costs for EDSS9 were the same as for EDSS8. At all levels of disability, indirect costs comprised more than half of total costs (**Figure 2**). More details can be found in the original publication (https://www.msaustralia.org.au/wp-content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf).

Figure 2. Estimated annual costs per individual with all phenotypes of MS based on the Australian multiple sclerosis longitudinal study.




*EDSS = Kurtzke Expanded Disability Status Scale*

In NZ, OCR is given by quarterly infusion at the listed price of $9346 per vial ($37,384 per annum), (https://schedule.pharmac.govt.nz/ScheduleOnline.php?edition=&osq=Ocrelizumab). Vial sharing is unlikely and was not included in our analysis. Because the cost is subject to a confidential rebate, we varied the acquisition cost over a representative range of 10% to 90% of the list price in each analysis. Resources required for monitoring and administration of DMTs were applied to OCR as recommended in the package insert and costed according to Pharmac's standardised cost resource manual (https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/cost-resource-manual/). Other pharmaceuticals were included in the AMSLS but not specified by name or cost. **Table 1** shows other costs.

Table 1. Input parameters for the multistate Markov model.

| Item | Value | Comment |
|---|---|---|
| Age at diagnosis | 40 years (base case) | |
| EDSS distribution at start | ITT distribution in ORATORIO or EDSS3, 4 or 5 | ORATORIO |
| List price of OCR per vial | $9,346 | Pharmac[a] |
| Vials per 6-monthly dose of OCR | 2 | |
| Confidential rebate on list price | 10% to 90% | Assumed potential range |
| Annual cost of monitoring OCR | $468.78 | Pharmac Cost Resource Manual[b] |
| Cost of administration of OCR (y1) | $1,545.00 | |
| Cost of administration of OCR (y2+) | $1,030.00 | |
| Cost of IV methylprednisolone (y1)[c] | $102.30 | |
| Cost of IV methylprednisolone (y2+) | $68.20 | |
| Time from 2023 to biosimilar entry | 5 years (range 3 to 7 years) | Based on patent expiry in 2028 in Europe & 2029 in the USA (Roche Products Ltd) |
| Biosimilar discount off rebated price of OCR | 70% | Based on Pharmac experience |
| Efficacy of OCR (hazard ratio) | 0.76 (0.59-0.98) | ORATORIO |
| Withdrawal rate in y1 (2+) | 0.078 (0.05) | ORATORIO follow up (Roche Products Ltd) |
| Annual discount rate | 3.5% (base case); 3% or 5.0% | For both costs and benefits |

*a Pharmac. https://schedule.pharmac.govt.nz/ScheduleOnline.php?edition=&osq=Ocrelizumab*
*b Pharmac.https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/cost-resource-manual*
*c Prophylaxis with analgesic or antipyretics plus antihistamine is recommended but the cost is minor*

## 2.5 Treatment with ocrelizumab

Based on findings for the primary endpoint in the ORATORIO clinical trial (12-week confirmed disability progression), the impact of OCR was estimated by multiplying each forward transition probability in EDSS states 2.0 to EDSS 6.0 by a hazard ratio of 0.76 (95% CI 0.59–0.98) [13, 15].(https://www.nice.org.uk/guidance/ta585/evidence/appraisal-consultation-committee-papers-pdf-6786071101). Our base case model assumes that treatment with OCR is withdrawn in EDSS states above 6.0. Treatment discontinuations were experienced by 4.1% in the OCR arm and 3.3% in the placebo arm of ORATORIO [13]. These were included as a branch in the model (see Figure 1 above).

In the ORATORIO clinical trial, there was no statistically significant difference between groups in the rates of serious adverse events and infections, and discontinuation rates due to serious adverse events were similar in treated and placebo groups [13]. Long-term clinical information up to 10 years post marketing (to November 2022) showed that adverse event rates of OCR in 13 clinical trials remained stable in the long-term (https://www.ocrelizumabinfo.global/en/homepage/updated-safety-analysis.html). Given this information, the cost and disutility due to adverse events for patients who continue therapy with OCR were not included in the model.

## 2.6 Wheelchair dependence

To obtain the time to wheelchair dependence, the model was collapsed into two states: EDSS 0 to 6 (ambulant) versus all others including deaths. The median time to the wheelchair dependence/death state was then obtained from the Markov trace.

## 2.7 Cost-utility analysis

Cost-utility analysis is undertaken by Pharmac and agencies in other countries to inform funding decisions for costly novel pharmaceuticals. For this study, the incremental cost-effectiveness ratio (ICER) is defined as the lifetime net cost per lifetime gain in quality-adjusted life years (QALYs), with all costs and benefits discounted to net present value at 3.5% annual discount rate (https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/economic-analysis/prescription-for-pharmacoeconomic-analysis-methods-for-cost-utility-analysis/). The present analysis models the intention to treat (ITT) cohort in the ORATORIO clinical trial, consistent with Pharmac's prescribing criteria (https://schedule.pharmac.govt.nz/2024/06/01/SA2273.pdf).

## 2.8 Net monetary benefit

'Net monetary benefit' is a variant of traditional cost benefit analysis (CBA). The underpinning theory of CBA is that the outcome measure must include the effects of an intervention on everyone in society [27]. New Zealand Treasury has developed a CBA toolkit 'CBAx' for considering a wide range of impacts across time and multiple dimensions (https://www.treasury.govt.nz/sites/default/files/2023-12/cbax-model-dec2023.xlsx). Health benefits are converted into monetary form using a standardised conversion factor. On this metric, a product or service is potentially fundable if its ICER is less than the monetary value of a QALY.

A QALY in Treasury's CBAx 'Impacts' database is valued at $NZD43,313 based on Pharmac's historical investments or $NZ120,200 based on the societal value of a statistical life ($9.83m) (https://www.treasury.govt.nz/information-and-services/state-sector-leadership/investment-management/plan-investment-choices/cost-benefit-analysis-including-public-sector-discount-rates/treasurys-cbax-tool). These figures represent healthcare and societal bounds of the Treasury's guidance on publicly acceptable values of a QALY for cost effective funding.

Economic analyses by Pharmac are conducted from a healthcare perspective, although NZ Treasury recommends taking a societal perspective. We provide analyses from both perspectives, as recommended by the Second Panel on Cost Effectiveness in Health and Medicine [28]. For new pharmaceuticals, the supplier provides a list price, and the funder (Pharmac) negotiates a confidential rebate. Therefore, model outputs were determined over a wide range of acquisition costs. R

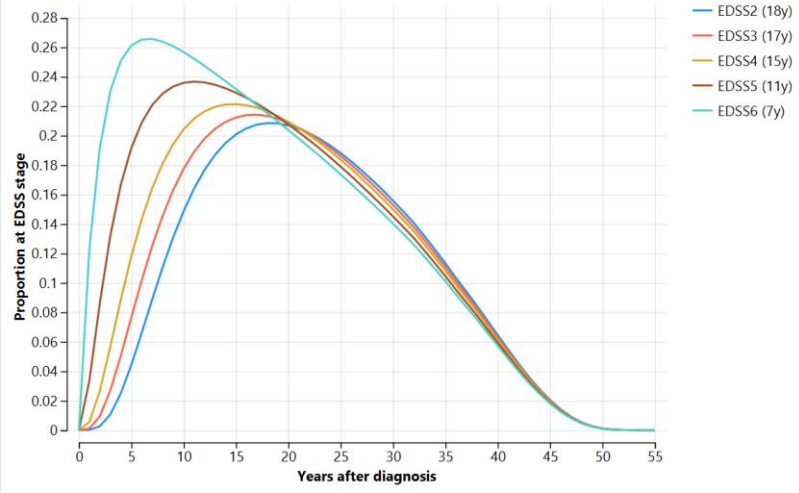
All research methods and analyses were aligned with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [29].

# 3. RESULTS

## 3.1 Time to wheelchair dependence

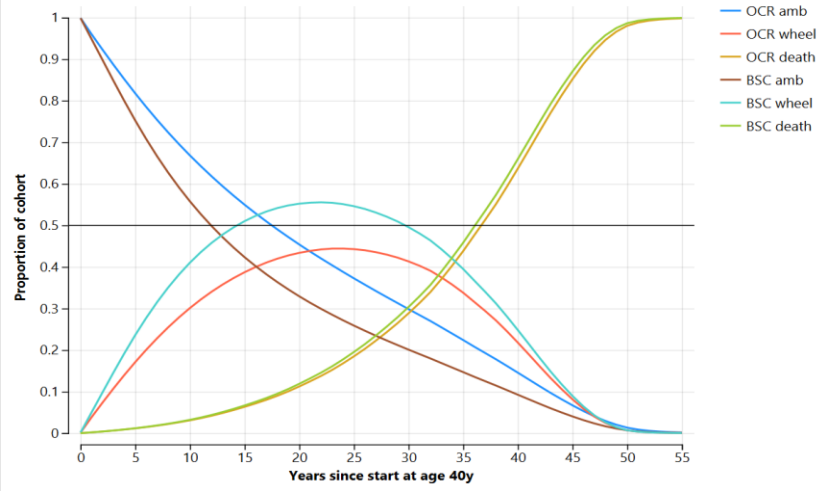
Long-term disability is a very important outcome of MS. In the base case analysis, the cohort model starts at 40 years of age. The modelled time to the peak prevalence of health state EDSS7 (wheelchair dependence) or death from any cause is 18 years if PPMS is diagnosed at EDSS2 but only 7 years if diagnosed at EDSS6 **(Figure 3).** All graphs decline after the peak because some of the survivors progress to higher EDSS levels or die from MS or another cause.

Figure 3. Proportions of the BSC cohort that progresses to EDSS7 or higher EDSS levels or death.




For a modelled cohort 40 years of age starting at the ORATORIO ITT initial distribution of EDSS states, 50% of the BSC cohort is still ambulant at 12 years, 46% are wheelchair dependent and the remainder have died**.** For the OCR-treated cohort, 50% of the cohort is still ambulant at 17 years and 41% are wheelchair dependent **(Figure 4).** Correspondingly, 62% of the treated cohort is ambulant at 12 years and 34% is wheelchair dependent.

Figure 4. Proportions of the cohort ambulatory (Amb), wheelchair dependent (wheel) or deceased for ORATORIO ITT cohorts treated with ocrelizumab (OCR) or best supportive care (BSC).




The time to wheelchair dependency ranges from 7 to 17 years depending on the EDSS at diagnosis. OCR delays this by 4.0 to 6.0 years depending on the EDSS when treatment begins **(Table 2)**.

Table 2. The median time in years to EDSS7+ (wheelchair dependency or death) in a treated versus control cohort starting at EDSS 2 to 6.

| Starting EDSS | Best supportive care | Ocrelizumab | Delay (years) |
|---|---|---|---|
| 2 | 17.0 | 23.0 | 6.0 |
| 3 | 15.0 | 21.5 | 6.5 |
| 4 | 13.5 | 19.5 | 6.0 |
| 5 | 10.5 | 16.0 | 5.5 |
| 6 | 7.0 | 11.0 | 4.0 |
| ORATORIO ITTa | 12.0 | 17.5 | 5.5 |

*a Initial distribution: EDSS2=0.003; EDSS3=0.2485; EDSS4=0.2783; EDSS5=0.1889; EDSS6=0.2783*

## 3.2 Cost effectiveness

At the three acquisition costs shown, OCR is substantially more cost-effective from a societal than a healthcare perspective. It is more cost-effective when therapy commences at a younger than older age, suggesting the value of early diagnosis and treatment. In the base case (50% of list price; therapy commences at age 40y; the initial ITT distribution of EDSS levels and hazard ratio 0.76, in ORATORIO [13]) the healthcare ICER is 42% higher than that from a societal perspective. At 10% of the list price from a societal perspective, at 30 or 40 years of age, OCR dominates BSC (i.e. provides incremental benefits to patients and is cost-saving to society). At 50% of list price the ICER (at starting age 40 years) is $98,490 per QALY gained from a societal perspective, and from the narrower healthcare perspective, at just 10% of the list price the ICER is $NZ35,290 **(Table 3**).

Table 3. Incremental cost effectiveness ratios (2022 NZD per QALY) of ocrelizumab by study perspective and age at commencement of therapy, at 3 acquisition costs.

| | Percent of list price ($37,384 pppa = $US22,356) | | |
|---|---|---|---|
| Perspective | 10% | 50% | 90% |
| *Age at commencement of therapy 30y (1.061 QALYs)* | | | |
| Healthcare | $30,916 | $126,543 | $222,170 |
| Societal[a] | Dominant | $82,588 | $178,215 |
| *Age at commencement of therapy 40y (0.931 QALYs)* | | | |
| Healthcare | $35,290 | $139,986 | $244,682 |
| Societal[a] | Dominant | $98,490 | $203,186 |
| *Age at commencement of therapy 50y (0.760 QALYs* | | | |
| Healthcare | $42,574 | $163,079 | $283,585 |
| Societal[a] | $4,322 | $124,827 | $245,333 |

*ORATORIO ITT cohort, annual discount rate 3.5%; pppa = per person per annum; age at start 40y*
*a Healthcare costs plus direct non-medical costs including special equipment, house/car modifications and informal care plus productivity losses*

At any given drug acquisition cost, the ICER is more cost effective at lower starting age or EDSS states. At 10% list price, therapy is dominant for the cohort from a societal perspective but not from a healthcare perspective **(Table 4).**

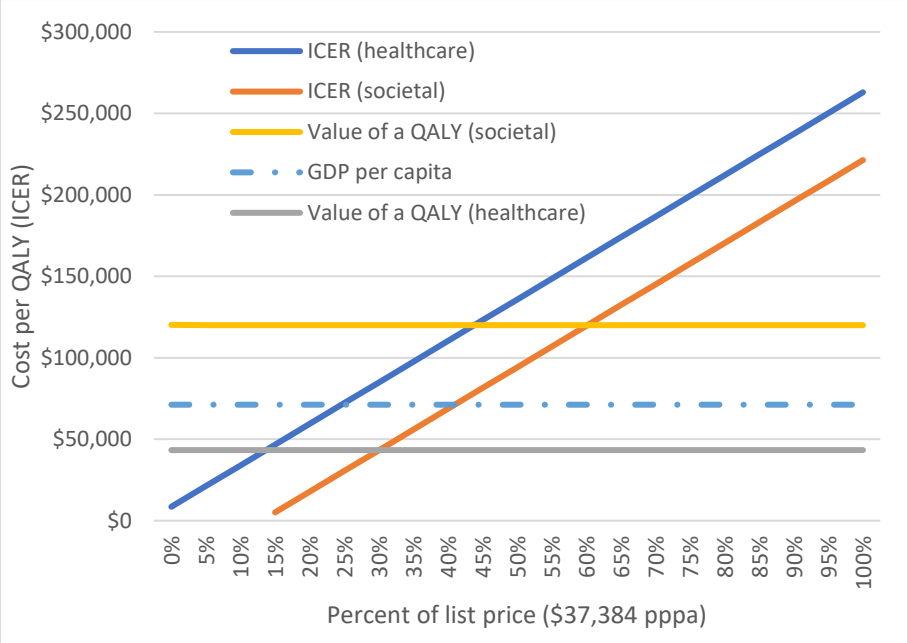
Table 4. Incremental cost effectiveness ratio varies with the study perspective and the acquisition cost of ocrelizumab.

| EDSS at start of therapy | QALYs gained | Incremental cost effectiveness ratio | | | | | |
|---|---|---|---|---|---|---|---|
| | | Societal perspective[a] | | | Healthcare perspective | | |
| Percent of list price | | 10% | 50% | 90% | 10% | 50% | 90% |
| ORATORIO[b] | 0.931 | Dominant | $98,490 | $203,186 | $35,290 | $139,986 | $244,682 |
| EDSS3 | 1.091 | | $78,350 | $177,802 | $33,022 | $132,473 | $231,924 |
| EDSS4 | 1.004 | | $93,175 | $196,722 | $34,533 | $138,079 | $241,626 |
| EDSS5 | 0.903 | $572 | $106,124 | $211,677 | $35,143 | $140,695 | $246,248 |

*Starting age 40y; hazard ratio 0.76; discount rate 3.5%; list price of OCR $9346 per vial (4 vials pppa); age at start 40y; Dominant = lower lifetime cost than BCR, and patient benefits*
*a Healthcare costs plus direct non-medical costs including special equipment, house/car modifications and informal care plus productivity losses. b ORATORIO initial distribution of EDSS states (ITT analysis)*

There is a linear relationship between the ICER and the acquisition cost of OCR **(Figure 5).** The ICER is approximately equal to Treasury's suggested societal threshold (NZD $120,200) when it costs 59% of the list price (viz. $22,057 per annum) or the healthcare threshold ($43,313) when it costs 12.5% of the list price ($4673 per annum). Alternatively, an acquisition cost of 39.6% of list price ($14,804) could be justified if the criterion of gross domestic profit (GDP) per capita ($71,183 in 2022) is used as a funding threshold, as it is elsewhere (see the Discussion).

Figure 5. The relationship between the lifetime incremental cost-effectiveness ratio (ICER) and annual acquisition cost of OCR, from both a healthcare and a societal perspective.




*Hazard ratio 0.76, annual discount rate 3.5%, age at commencement of therapy with OCR 40y*

## 3.3 Sensitivity analyses on cost utility analyses

### 3.3.1 One way sensitivity analyses

Several features emerge from a series of one-way sensitivity analyses (**Table 5).** At the high end of efficacy (95% CI of the hazard ratio in ORATORIO), at 50% of the listed price the societal ICER is $NZ27,062 and at 90% of list price it is $85,093. However, from a healthcare perspective at any price, the ICER is much higher. Using the MRI-confirmed starting cohort in ORATORIO instead of the ITT cohort, or changing the source of HSUs, has only a minor impact on the ICER.

Importantly, the cost effectiveness of therapy with OCR depends strongly upon the cost and timing of a biosimilar that is very likely to enter the market at patent expiry. The ICER is moderately sensitive to the cost of management of MS from a societal perspective, but not from a healthcare perspective, because of inclusion or exclusion of indirect costs, respectively. From both perspectives, the results are sensitive to the efficacy and cost of OCR, age at commencement of therapy, the time of entry of a biosimilar pharmaceutical and the discount rate. The ICER is relatively insensitive to changes in the sources of health state utilities. Extending treatment from EDSS6 to EDSS7 slightly improves its overall cost effectiveness. The NICE reference case includes caregiver disutility in technology appraisal (https://www.valueinhealthjournal.com/action/showPdf?pii=S1098-3015%2818%2934434-6). Inclusion of caregiver disutility for MS has a modest effect on the ICER . We also explored the possibility of treatment efficacy waning by 20% after 5 years. This raised the ICER by 23% from a societal perspective and 16% from a healthcare perspective.

Table 5. Sensitivity of the ICER (2022 $NZD per QALY) to study perspective, ocrelizumab price, discount rate and costs and other factors (2022 NZD).

| | Societal perspective[a] | | | Healthcare perspective | | |
|---|---|---|---|---|---|---|
| | Percent of list price | | | Percent of list price | | |
| | 10% | 50% | 90% | 10% | 50% | 90% |
| *Hazard ratio (HR)* | | | | | | |
| 0.76 (base case) | Dominant | $98,490 | $203,186 | $35,290 | $139,986 | $244,682 |
| 0.59 (high efficacy) | | $27,062 | $85,093 | $14,429 | $72,460 | $130,491 |
| 0.98 (low efficacy) | >>$150,000 | >>$150,000 | >>$150,000 | >>$150,000 | >>$150,000 | >>$150,000 |
| *Cost of management (3.5% discount rate, HR 0.76* | | | | | | |
| Low cost (-30%) | $10,060 | $114,756 | $219,452 | $39,107 | $143,803 | $248,499 |
| High cost (+30%) | Dominant | $82,225 | $186,921 | $31,473 | $136,169 | $240,865 |
| *Time to biosimilar entry (societal perspective, discount rate 3.5%, base case 5 years, HR 0.76 )*[b] | | | | | | |
| 3 years | Dominant | $76,859 | $164,250 | $30,964 | $118,355 | $205,746 |
| 7 years | | $117,089 | $236,664 | $39,010 | $158,585 | $278,160 |
| *Health state utility source* | | | | | | |
| SW England | Dominant | $101,313 | $209,010 | $36,302 | $143,999 | $251,696 |
| UK | | $110,942 | $228,874 | $39,752 | $157,684 | $275,616 |
| *Time to biosimilar entry (societal perspective, discount rate 3.5%, base case 5 years, HR 0.76)*[b] | | | | | | |
| 3 years | Dominant | $76,859 | $164,250 | $30,964 | $118,355 | $205,746 |
| 7 years | | $117,089 | $236,664 | $39,010 | $158,585 | $278,160 |
| *Cost of biosimilar*[c] | | | | | | |
| 50% discount | $1,002 | $134,529 | $268,056 | $42,498 | $176,025 | $309,552 |
| 90% discount | Dominant | $62,452 | $138,317 | $28,083 | $103,948 | $179,813 |
| *Other* | | | | | | |
| Include carer disutility[d] | Dominant | $85,644 | $176,684 | $30,687 | $121,727 | $212,767 |
| Treat to EDSS7 | $1,686 | $102,163 | $202,640 | $35,961 | $136,438 | $236,915 |
| MRI cohort | Dominant | $98,609 | $203,287 | $35,258 | $139,937 | $244,615 |
| Linear SMR | Dominant | $96,416 | $202,873 | $35,223 | $141,681 | $248,138 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Efficacy wanes 20% after 5y | $278 | $120,716 | $241,153 | $42,170 | $162,607 | $283,044 |
| Discount rate 5% | Dominant | $118,347 | $241,945 | $41,687 | $165,286 | $288,884 |
| Discount rate 3% | | $92,621 | $191,476 | $33,343 | $132,198 | $231,054 |

*SMR = standardised mortality ratio*
*a Healthcare costs plus direct non-medical costs including special equipment, house/car modifications and informal care plus productivity losses*
*b Patent expiry is 2028 in Europe and 2029 in the USA (Roche Products Ltd)*
*c Discounted off the rebated list price of ocrelizumab*
*d Carer disutility for MS from manufacturer submission TA127 to NICE based on carers for Alzheimer's disease adjusted for carer time in MS (http://www.nice.org.uk/guidance/ta127)*

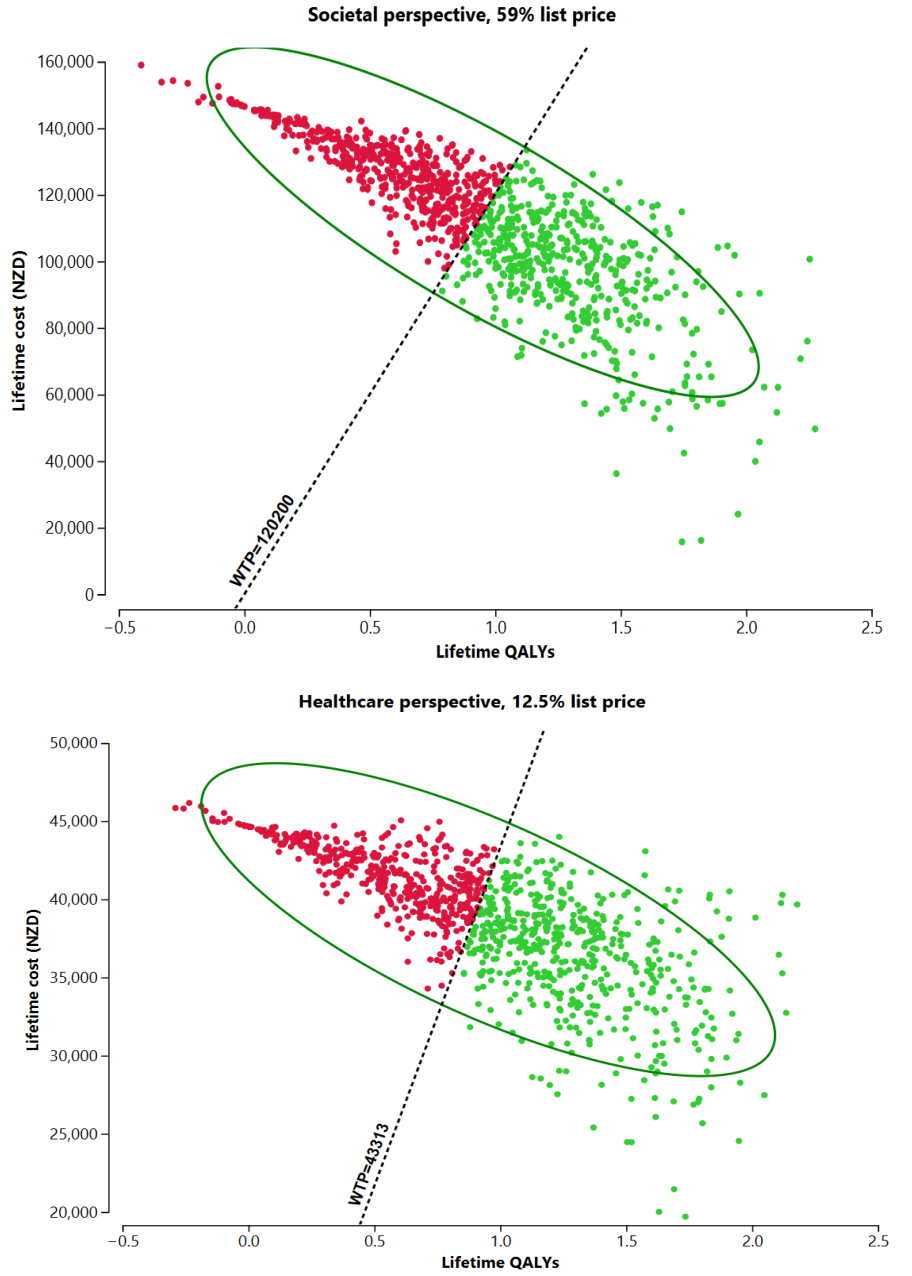
### 3.3.2 Probabilistic sensitivity analysis

In a probabilistic sensitivity analysis (PSA), repeated random samples are taken from distributions of uncertain variables. The expected cost and QALY for each pair of values is then plotted on a scatter graph. The probability of the treatment being cost effective is given by the proportion of samples for which the ICER is less than the WTP [30].

Because transition probabilities for BSC comprise a 10-x10 matrix rather than individual values, we modified the original model for a PSA. For the treatment transition matrix, all 45 individual forward transition probabilities (from EDSS 0 to 6) in the control (BSC) transition matrix were multiplied by the hazard ratio from ORATORIO (0.76), which was given a lognormal distribution. A sensitivity analysis multiplier, which was applied simultaneously to all EDSS costs, was given a gamma distribution [30]. Mean values from these distributions were used in all analyses.

A total of 1000 replications are presented as scatter plots from both societal and healthcare perspectives (**Figure 6**). WTP thresholds derived from NZ Treasury recommendations are also shown (see the Methods). Notably, the discounted lifetime cost corresponding to one QALY is much higher from a societal than a healthcare perspective, although the distributions in the scatterplots are similar. Including an age distribution in place of age 40 years (PERT distribution; most likely age 40y, range 25y to 55y, slope 1) gave a very similar result (not shown).

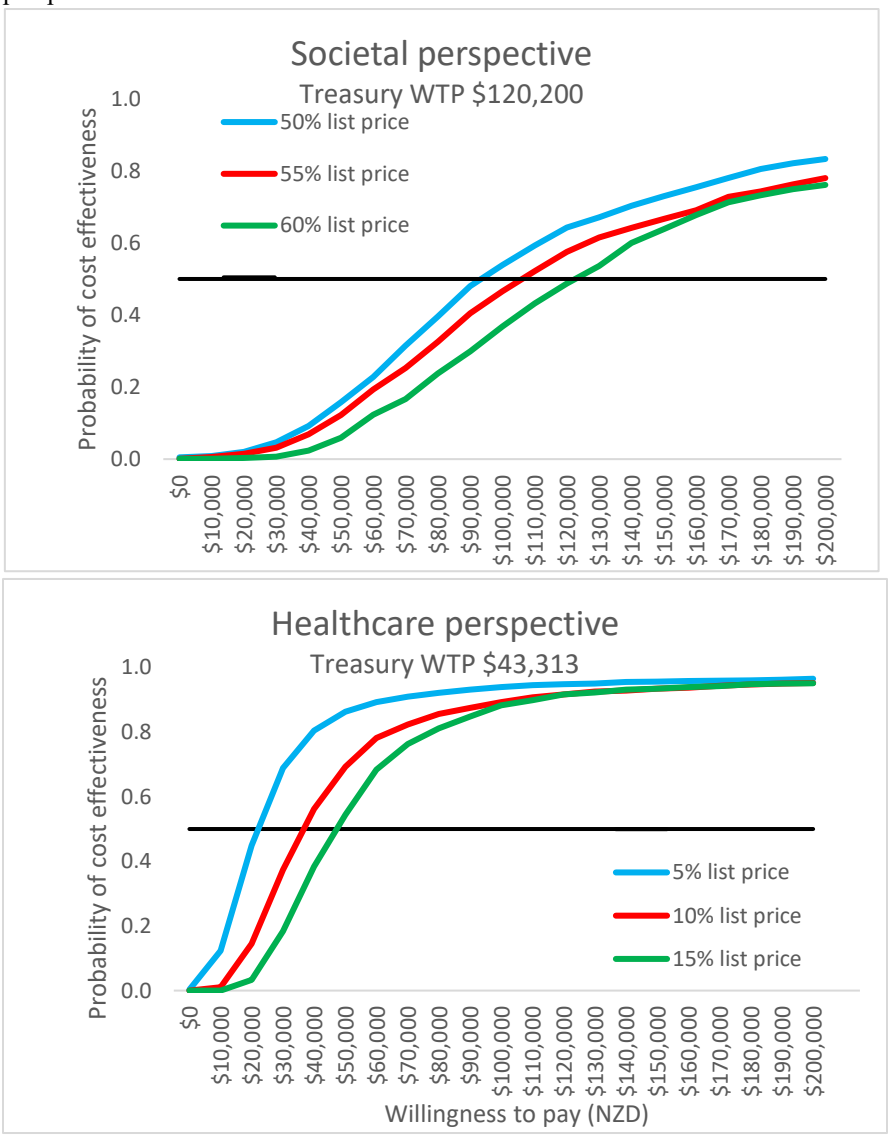
Figure 6. Incremental cost effectiveness scatter plot from both societal and healthcare perspectives, Note the different vertical scales. The acquisition cost at the willingness-to-pay threshold is the price at which the probability of cost effectiveness is 50%. Note the different vertical scales.



*List price: NZD $37,384 per patient per annum. Age 40 years. Lifetime QALYs 0.931. Hazard ratio: lognormal distribution (mean of logs -0.274, s.d. of logs of CI +0.129). Sensitivity analysis on costs: gamma distribution (mean 1.0, s.d. 0.2). WTP = willingness to pay.*

Cost-effectiveness acceptability curves illustrate the higher willingness to pay, from a societal compared to a healthcare perspective at various list prices of OCR (**Figure 7**). From each perspective, the bottom graph represents the suggested NZ Treasury funding threshold. Including an age distribution (PERT, most likely 40y, range 25y to 55y, slope 1) in the analysis had a very similar result (not shown). At 50% list price ($18,692), from a societal perspective with Treasury WTP threshold of $120,000, the probability of treatment with OCR being cost effective is 64%. At 10% of list price ($3,783) from a healthcare perspective with Treasury WTP threshold of $43,313, the probability of treatment with OCR being cost effective is 63%. Therefore treatment with OCR is equally cost effective at 50% of list price from a societal perspective or 10% of list price from a healthcare perspective.

Figure 7. Cost-effectiveness acceptability curves at 3 levels of drug acquisition cost, from societal and healthcare perspectives.



*List price: NZD $37,384 per patient per annum. Age 40 years. Lifetime QALYs 0.931. Hazard ratio: lognormal distribution (mean of logs -0.274, se of logs of CI +0.129). Sensitivity analysis on costs: gamma distribution (mean 1.0, s.d. 0.2).*

## 3.4 Net monetary benefit

Pharmac does not have a willingness to pay (WTP) funding threshold [31], but it does have 'factors for consideration' that include costs to society, although these are not quantified in its economic analyses [31, 32]. One alternative metric is NMB which is a summary statistic that represents the value of an intervention in monetary terms. NMB scales both health outcomes and use of resources to costs, so that comparisons can be made without defined ICERs (https://yhec.co.uk/glossary/net-monetary-benefit/).

NMB = (QALYs * WTP) – C (where WTP = willingness-to-pay threshold; C = discounted lifetime cost)

Positive values for NMB mean that therapy with OCR generates savings over the lifetime of the cohort. Using NMB as a decision metric, and if NZ society is willing to pay $NZ100,000 per QALY gained (achieving 10 QALYs per million dollars invested in healthcare), at 50% list price ($18,692) there is a theoretical monetary gain to society (positive NMB) but a modest cost to healthcare. The net monetary benefit of OCR is positive at 10% of list price from both perspectives at WTP $40,000 or higher, but negative at 50% of list price and higher **(Table 6).**

Table 6. Net monetary benefit of therapy with ocrelizumab (in 2022 NZD) over a range of hypothetical WTP thresholds and ocrelizumab prices, from both healthcare and societal perspectives.

| **Percent of list price** | **10%** | | **50%** | | **90%** | |
|---|---|---|---|---|---|---|
| QALYs | 0.931 | | | | | |
| Perspective | Healthcare | Societal[a] | Healthcare | Societal[a] | Healthcare | Societal[a] |
| Incr. cost | $32,866 | $5,779 | $130,371 | $91,725 | $227,876 | $189,230 |
| ICER | $35,302 | $6,207 | $140,033 | $98,523 | $244,765 | $203,255 |
| Threshold (WTP) | Net monetary benefit | | | | | |
| $40,000 | $4,374 | $31,461 | -$93,131 | -$54,485 | -$190,636 | -$151,990 |
| $60,000 | $22,994 | $50,081 | -$74,511 | -$35,865 | -$172,016 | -$133,370 |
| $80,000 | $41,614 | $68,701 | -$55,891 | -$17,245 | -$153,396 | -$114,750 |
| $100,000 | $60,234 | $87,321 | -$37,271 | $1,375 | -$134,776 | -$96,130 |
| $120,000 | $78,854 | $105,941 | -$18,651 | $19,995 | -$116,156 | -$77,510 |

*WTP = willingness to pay; hazard ratio = 0.76; discount rate 3.5%; list price of OCR = $NZ37,384 per annum; therapy commences at 40 years of age; ORATORIO ITT distribution of initial EDSS states*
*a Healthcare costs plus direct non-medical costs including special equipment, house/car modifications and informal care plus productivity losses; Positive values in italics.*

# 4. DISCUSSION

Our study is the first southern hemisphere, lifetime cost-effectiveness analysis of the treatment of people living with PPMS with OCR versus BSC from both healthcare and societal perspectives, using both cost-utility analysis and cost-benefit analysis. It also estimates the impact of OCR on the time from diagnosis to wheelchair dependence or death. Based on NZ Treasury criteria, OCR can be cost effective from both healthcare payer and societal perspectives, at different acquisition costs; and at relatively low acquisition costs it can provide overall cost savings to society. We also found that cost effectiveness improves when younger individuals are treated, and when individuals are treated earlier in their disease course. Importantly, the clinical imperative is increasingly shifting to earlier diagnosis and treatment with high efficacy DMTs [33, 34]. Unsurprisingly, the cost effectiveness of therapy with OCR is very sensitive to its acquisition cost of OCR, from either a healthcare or societal perspective. The ICER is moderately sensitive to the cost of best supportive care and the discount rate.

Our secondary objective was to determine the median time to wheelchair dependence or death (EDSS7+) and the delay in progression by OCR. With a cohort 40 years of age, the median time to EDSS7 or death is 12 years, and OCR delays this endpoint by 6 years. In a statistical analysis of the clinical trial ORATORIO, the median time to 24-week confirmed disability progression to EDSS7 in the placebo group was 12.1 years, compared to 19.2 years in the OCR-treated group, giving a delay of 5.1 years. [35, 36]. The authors of this study assumed a hazard ratio of 0.54, based on ORATORIO plus the extended control period. This gave them a longer delay than our model (see Table 2 above). The economics review group of NICE estimated a delay between 3.1 years and 9.2 years in ORATORIO, depending on the statistical model used [15]. For comparison, a study of 5779 individuals with PPMS reported that the time from onset of symptoms (at various EDSS levels) to EDSS6 was 14 years (95% CI 11.3 to 16.7y) [37]. This is longer, probably because symptom onset can occur some years before diagnosis. In contrast, a German study of DMT-naïve individuals with PPMS reported 'about 16 years' from diagnosis to EDSS7 although the sample size was modest [38]. In a study in Portugal, the time to EDSS7 for 37% of patients with PPMS reached an EDSS score of 7.0 after a mean (SD) follow-up of 10.6 (5.6) years [39]. Most of these findings are consistent with ours, giving confidence in our Markov model.

The multistate Markov model approach has been utilised by others to predict economic outcomes for the more prevalent forms of MS [40-45]. At the time of writing (September 2024) there is one published cost-utility analysis of OCR in patients with PPMS [46] which takes a US healthcare payer perspective, and a Portuguese cost-utility analysis which takes a societal perspective [47] and a NICE evidence group review of an unpublished pharmaceutical company model [15]. Our model was developed for the funding situation in New Zealand, but the methodology has relevance to other countries with similar funding criteria for publicly funded pharmaceuticals.

## 4.1 Perspectives and funding criteria

The goal of taking a societal rather than healthcare perspective is to maximize social welfare from a flexible rather than a siloed healthcare budget. In this context, impacts on society that fall outside the healthcare sector are also included in the decision-making process. Most guidelines from well-established funding agencies recommend inclusion of a societal perspective and it is defined in 73% of these [17]. It is also recommended in most other areas of NZ government like transport policy and environmental policy.

Unlike reimbursement agencies in other jurisdictions, Pharmac does not have a WTP funding threshold [31], although it does have 'factors for consideration' which include costs to society, although these are not quantified in its economic analyses [31, 32]. There is an ongoing debate about the choice of WTP cost-effectiveness thresholds that is crucial in determining the value of healthcare interventions and a jurisdiction's willingness to pay. The World Health Organization suggests that the WTP threshold per QALY could be in the range of 1 to 3 GDP per capita [48]; however, 97% of 174 countries studied recently had a WTP threshold less than one GDP per capita. The estimated WTP

threshold for Australia, Canada, Germany and the UK ranged from $US38,000-$US50,000 [49]. In our analysis, from a societal perspective the ICER for OCR is equal to the (estimated) 2022 NZ GDP per capita ($NZ71,183 or ) at 39.6% of list price ($14,804). Alternatively, by NZ Treasury criteria, Pharmac can be justified in paying up to $22,057 per person per annum for treatment of PPMS with OCR, when considering all the lifetime costs and benefits at net present value. However, when considering only those costs for healthcare, investment in OCR could be justified only up to $4,636 per person per annum.

Pharmac has historically made positive funding decisions over a broad range of ICER levels including those reported in this study. This is evidenced in part by the investment in OCR for PPMS being announced while this study was in progress. Pharmac now operates with an independent appropriation from government, and so is obligated to follow the guidelines set out by New Zealand Treasury in budget bids for additional funds. For this, and to ensure comparability between government departments on investment options, it would seem sensible for Pharmac to report NMB according to the value of a QALY set by New Zealand Treasury. We have shown NMB over a range of potential thresholds and drug acquisition costs, as guidance for price negotiations. The methodology is applicable elsewhere.

If Pharmac's health technology analyses of new pharmaceuticals had been undertaken from a societal perspective, as in China, Denmark, France, Norway, Portugal, Spain, Sweden, Taiwan, Thailand and The Netherlands [18] that would change the ranking of new pharmaceuticals that are approved and waitlisted for funding from Pharmac's capped budget. In particular, it would favour those new medicines that reduce disability and/or suffering adequately to allow some patients to return to work and/or to work more productively. This would apply to many chronic illnesses including advanced cancer, MS, many other neurological diseases and other rare diseases.

Additionally, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommends an even broader societal perspective to incorporate new and novel elements of value in health economic evaluation including family spillovers, the value of hope, scientific spillovers and broader productivity impacts. Notably, ISPOR recommends the adoption of this even broader societal perspective to address the limitations of conventional cost-effectiveness analysis [50, 51]. Some health technology assessment bodies are now considering these broader elements [51] .

## 4.2 Strengths and limitations

The main strength of our analysis is that it is built on a comprehensive and detailed set of both direct and indirect costs and HSUs. Also, the economic model was calibrated to the mortality of PPMS in New Zealand [20] which provides face validity. The calibration process necessitated developing a methodology for estimating the relationship between SMR and EDSS.

### 4.2.1 Costs

Because detailed New Zealand costs are not available, our analysis utilised a subset of the Australian MS longitudinal study consisting of 488 individuals who recorded their costs. In this regard, the results are only as accurate as the information provided by these individuals. Also, because the Australian study utilised only 4 levels of disability severity [none, mild (EDSS<4); moderate; severe (EDSS>6)] we interpolated between the levels. A more comprehensive study could be considered for New Zealand using the integrated data infrastructure (IDI), which links health databases with other databases through unique identifiers.

Total annual costs per individual for a small subset of individuals with PPMS in the Australian study (N=39) were similar to those in the parent study (N=448) although informal care costs comprised a much smaller proportion of the total cost of PPMS than for all MS combined, and the proportion of indirect costs through loss of productivity was much larger, especially at high levels of disability (https://www.msaustralia.org.au/wp-

content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf.) This does not affect our analysis materially because our analysis is independent of the relative proportions of direct non-medical costs versus indirect costs. Some Australian costs (such as hospitalisation) are likely to be higher than in New Zealand, and the healthcare system has a larger component of private funding, mostly through health insurance. However, our analysis did not attempt to differentiate public from private funding, and our findings are only moderately sensitive to the cost of illness.

For comparison, Thompson and colleagues (2017) reported UK costs of MS in 2015 taken from a UK subset of a large study throughout Europe. In contrast to the Australian study (and therefore ours), the cost rose exponentially with the severity of disability, and informal care accounted for over one-third of the cost of the most severe disability category. The study also reported that income lost through early retirement was substantial throughout the range of EDSS [26].

### 4.2.2 Health state utilities

Our study utilised European HSUs because New Zealand HSUs are sparse. We assumed that EDSS-specific HSUs measured across all phenotypes of MS could be applied to PPMS, based on the AMSLS [22] although they could arguably be slightly lower for PPMS [52]. Carer quality-of-life can be greatly impaired relative to the general population [53, 54]. Carer HSUs were derived from a population of carers providing care for people with Alzheimer's disease and adjusted to reflect the time spent providing care for people with multiple sclerosis. (https://www.nice.org.uk/guidance/ta585/evidence/). However, because HSU data for MS carers have not been validated to our knowledge, we included this factor only in a sensitivity analysis. It improved the cost effectiveness of OCR in PPMS and it would be expected to do the same for other therapies that delay disability progression.

## 4.3 Model scope and uncertainty

OCR was funded in New Zealand in October 2023 for treatment of PPMS from EDSS0 to EDSS6.5 (https://schedule.pharmac.govt.nz/2024/06/01/SA2273.pdf). Our model covered the range of EDSS0 to 6.0, but EDSS6.5 was not included because transition probabilities for EDSS6.5 are not available. However, when the model is extended to EDSS7 (wheelchair dependency), the ICER declines, suggesting that treatment with OCR up to EDSS6.5 would be at least as cost effective as stopping treatment after EDSS6 was reached.

There is no evidence that the treatment effect (hazard ratio) is the same for all EDSS transitions (https://www.nice.org.uk/guidance/ta585/evidence/appraisal-consultation-committee-papers-pdf-6786071101) but that is a limitation of the clinical trial, which flows through to our analysis and others. Potential waning of the treatment effect by 20% after 5 years of treatment reduced the cost effectiveness of treatment. There is evidence that treatment with some DMTs including OCR becomes less effective in older patients [55] although there is insufficient information for OCR to model this convincingly. Futher research is required.

Our study did not include the cost of adverse effects of therapy with OCR. A large post marketing study of OCR reported that continuous administration of OCR for up to 7 years in clinical trials, as well as its broader use for more than 3 years in the real-world setting, was associated with a 'favourable and manageable safety profile' without emerging safety concerns, in a heterogeneous MS population [56]. As of March 2024, more than 350,000 patients with RMS or PPMS have been treated with OCR globally. There have been 16 confirmed cases of progressive multifocal leukoencephalopathy (PML) in patients with MS, of which 12 were carry-over cases from prior disease-modifying therapies (Roche Products - Data on File, June 5, 2024). Therefore the impact of including the cost of managing PML in the analysis is likely to be trivial, although some case series have reported increased rates of hospitalisation with infection in older, more disabled MS patients [57]. Weber and colleagues in an uncontrolled cohort study of OCR to December 2020 reported that in Germany the most common and serious adverse events were infections and infestations, with serious infection rates of 1.5 events per 100 patient years for patients with PPMS [58]. It is difficult to cost these convincingly, given the uncontrolled study and limited detail on the types of infection.

Our findings are sensitive to the acquisition cost of OCR and its efficacy over time; healthcare and other costs; the age at treatment commencement; the cost and timing of a potential biosimilar pharmaceutical; and the discount rate; and moderately sensitive to the level of disability (EDSS) when treatment begins. Long-term clinical information is required to establish whether treatment effects wane over time, and to determine long-term adverse effects of therapy. Either of these would reduce the cost effectiveness of therapy to an unknown extent.

## 4.4 Conclusions

In conclusion, treatment of PPMS with OCR is accompanied by a delay in wheelchair dependence or death which is larger when treatment begins at younger age or lower levels of disability. OCR appears considerably more cost-effective from a societal than a healthcare perspective, therefore a funding decision depends critically upon the study perspective. This study illustrates the importance of taking non-medical and indirect costs into account when evaluating new pharmaceuticals for chronic illnesses that require significant resources outside of healthcare budgets.

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# 6. SUPPLEMENTARY INFORMATION

## S1. Mortality

The standardised mortality ratio (SMR) is an average value across all EDSS health states; but mortality increases steeply with more severe disease [59]. Therefore it was necessary to develop a function relating SMR to EDSS. Applying UK average SMR values to EDSS states [59] gave implausibly high mortality for older age groups with severe MS, so this approach was discarded. Therefore an exponential function of the form SMR = exp(α*EDSS) was developed to express the increasing relationship between SMR and EDSS state. We assumed that mortality for health state EDSS0 (no disability) is equivalent to that of the general population [(https://infoshare.stats.govt.nz/), adjusted to 59% female [5]. The exponential function was then multiplied by sex-adjusted population mortality at each age and converted to a probability [Prob = 1-exp(-Rate)]. The parameter α was set to 0.14 to give a life expectancy that was 9 years less than that of the sex-adjusted general population [5]. Fot a sensitivity analysis, the exponential function was replaced with a linear function bounded at SMR = 3.3 for EDSS9, which gives the same 9-year life expectancy deficit as the exponential function (**Table S1**).

*Table S1. Standardised mortality ratio at each EDSS state, comparing a linear model with an exponential model*

| EDSS | Linear[a] | Exponential[b] |
|---|---|---|
| 0 | 1.00 | 1.00 |
| 1 | 1.26 | 1.15 |
| 2 | 1.51 | 1.32 |
| 3 | 1.77 | 1.52 |
| 4 | 2.02 | 1.75 |
| 5 | 2.28 | 2.01 |
| 6 | 2.53 | 2.32 |
| 7 | 2.79 | 2.66 |
| 8 | 3.04 | 3.06 |
| 9 | 3.30 | 3.53 |
| Mean | 2.15 | 2.03 |

*Reference: general population at age 40 years*
a Boundaries 1.0 and 3.3 with linear interpolation
b Exp(0.14xEDSS)

## S2. Costs

The cost of illness at 4 levels of disability was estimated from the Australian Multiple Sclerosis Longitudinal Study, using 2017 purchasing power parity (PPP) ratio multiplied by the product of NZ consumer price indices from 2017 to 2022 (**Table S2**).

*Table S2. Mean annual costs per individual with multiple sclerosis by level of disability in Australia in 2017, adjusted to 2022 NZD (N=488).*

| | None (21%) | Mild (25%) | Moderate (35%) | Severe (18%) |
|---|---|---|---|---|
| *Direct medical costs* | | | | |
| Prescription pharms[a] | 103 | 477 | 305 | 1351 |
| Non-prescription pharms | 233 | 294 | 267 | 535 |
| Non pharma medical | 876 | 1197 | 1377 | 2675 |
| Health professionals | 1632 | 2017 | 3037 | 3859 |
| Community care | 796 | 1922 | 2954 | 7519 |
| Hospital stays | 1251 | 4364 | 2386 | 3504 |
| Sub total | 4890 | 10271 | 10325 | 19443 |
| *Direct non-medical costs* | | | | |
| Special equipment | 141 | 368 | 1059 | 2719 |
| Alterations to car/home | 478 | 1680 | 4154 | 6953 |
| Transport | 354 | 573 | 1165 | 2637 |
| Informal care | 0 | 3971 | 12109 | 16401 |
| Sub total | 973 | 6592 | 18488 | 28710 |
| *All direct costs* | *5863* | *16863* | *30128* | *48695* |
| *Indirect costs* | | | | |
| Lost productivity | 2093 | 3569 | 4161 | 1640 |
| Lost wages | 7195 | 23814 | 34699 | 30218 |
| Sub total | 9288 | 27383 | 38860 | 31858 |
| *TOTAL* | *15151* | *44246* | *68988* | *80553* |

a The cost of DMTs was subtracted because these were not funded for treatment of PPMS in NZ until October 2023.

Sources:
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