Key considerations in reimbursement decision-making for multiple sclerosis drugs in Australia

Yen Hoang Le Phan[a], Richard De Abreu Lourenco[a], Marion Haas[a], Naomi van der Linden[a,1]

[a]Centre for Health Economics Research and Evaluation, University of Technology Sydney, PO Box 123 Broadway NSW 2007, Australia.

[1]Naomi van der Linden was working at the Centre for Health Economics Research and Evaluation, University of Technology Sydney, while the work was performed. She is currently employed as Health Economics Manager at AstraZeneca Netherlands, Naomi.vanderLinden@astrazeneca.com.

Corresponding author:

Richard De Abreu Lourenco

Richard.DeAbreuLourenco@chere.uts.edu.au

Phone: +61 2 9514 4729

ORCIDs:

Yen Hoang Le Phan:	N/A
Richard De Abreu Lourenco:	0000-0002-5978-8774
Marion Haas:	0000-0002-9726-3063
Naomi van der Linden:	0000-0003-1646-9834

Abstract

Background: In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) advises on the reimbursement of drugs to be subsidised through the Pharmaceutical Benefits Scheme (PBS). This study aims to provide insights into the PBAC process and key considerations regarding the reimbursement of MS drugs in Australia.
Methods: The factors considered by the PBAC and its advice on whether to reimburse a drug are documented in public summary documents (PSDs). Qualitative content analysis of PSDs was conducted for all MS drugs considered by the PBAC between January 2006 and January 2018. Key issues identified by the PBAC were extracted and categorised. Common issues were identified and compared between drugs indicated for MS.
Results: A total of 23 submissions were evaluated relating to 13 MS drugs. Eight were recommended for reimbursement; an approval rate of 35% per submission and 62% per drug. Approval rates were higher for disease modifying treatments (73% per drug) than for other drugs (0% for nabiximols and fampridine submissions). The most frequently discussed issues in PSDs, irrespective of PBAC decision, were: (1) the validity of the indirect comparisons formed (n=11); (2) the validity of the approach to obtain utilities (n=6); (3) the lack of appropriate/long-term safety data (n=8); and (4) the time horizon used in the economic models (n=3).
Conclusion: A small but important number of issues have been consistently identified by the PBAC in relation to submissions for reimbursement of MS drugs. Drug developers and clinical trial investigators who are aware of these issues will be able to anticipate data requirements for reimbursement decision-making and thus potentially improve the evidence submitted for listing of MS drugs in Australia.

Keywords

Multiple Sclerosis; pharmaceutical reimbursement, decision-making.

Abbreviations

CHMP, Committee for Medicinal for Human Use; ICER, incremental cost-effectiveness ratio; MCID, minimal clinically important difference; MS, multiple sclerosis; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PSD, public summary document; QALY, quality-adjusted life year; RPBS, Repatriation Pharmaceutical Benefits Scheme; RRMS, relapsing-remitting multiple sclerosis; RSA, risk-sharing arrangement.

1. Introduction

In the past two decades, remarkable advances have been made in treatment options for multiple sclerosis (MS) [1]. These advances have been made hand-in-hand with considerable increases in spending on MS treatments by patients, healthcare payers and society as a whole [2]. For example, in Australia, the number of patients accessing government-subsidised drug treatment for relapsing-remitting MS (RRMS) increased from 8,630 in 2006 to 15,704 in 2014 [3]. Based on the published prices for RRMS therapies, this resulted in an increase in the net cost to the Australian Commonwealth from AUD$91m in 2006 to over AUD$288m in 2014 [3].

In Australia, drug reimbursement is provided through the Pharmaceutical Benefit Scheme (PBS), a scheme which aims to provide universal, affordable access to prescription medicines. Before drugs can be listed on the PBS, they must be assessed by the Pharmaceutical Benefits Advisory Committee (PBAC), an expert advisory committee which evaluates pharmaceuticals for their comparative clinical effectiveness, safety, and cost-effectiveness. Under Australian legislation, the PBAC is responsible for assessing requests to list new drugs, as well as significant changes to currently listed drugs on the PBS [4,5]. PBAC recommendations enable the Australian Government to determine which drug technologies provide good value for money and should therefore be publicly subsidised [6].

The PBAC's recommendations are made transparent to the public by publishing them online as public summary documents (PSDs). The purpose of the PSDs is to provide contextual information pertaining to each recommendation. Albeit they are limited in terms of the amount and depth of information published, PSDs

provide insight into the factors and trade-offs the PBAC noted in arriving at its recommendations. They therefore represent a valuable source of information, allowing various stakeholders to learn about the issues of importance during the PBAC process [7,8].

Given the rapid pace of advancement in MS treatments, it is worth studying the issues PBAC considered in arriving at recommendations regarding MS drug reimbursement. Internationally, MS patients and their health care professionals have expressed concern about unmet needs in MS management, and barriers to personalised medicine due to current reimbursement policies [9]. While the PBAC's recommendations impact which drugs will get reimbursed, not much is known about the key hurdles within the PBAC processes for MS drugs to be listed speedily for access by the Australian public.

This study provides a review and descriptive analysis of PSD's for MS treatments. The project aims to provide insights into the reimbursement process and key considerations by the PBAC regarding MS drugs. The results may facilitate understanding by clinicians, drug manufacturers and other stakeholders regarding the factors that influence reimbursement approval for MS drugs in Australia.

2. Methods

Current pharmacological treatment options for MS drugs were identified through the Australian Medicines Handbook 2017, the Australian Therapeutic Guidelines and the MS Australia website (https://www.msaustralia.org.au/about-ms/medications-treatments). PSDs of the identified drugs were obtained via the PBS Department of Health website under the heading "Public Summary Documents by Product", accessed in March 2017 and updated in March 2018.

Inclusion criteria were that the drug needed to have been considered by the PBAC between January 2006 and January 2018 and explicitly requested PBS listing as a treatment for MS (any stage). Treatments used for MS patients but where the submission to the PBAC did not specifically request MS as the indication (e.g. botulinum toxin type A, Botox®) were excluded. All relevant PSDs for MS drugs were selected, independent of whether they were a major or a minor submission[1].

A range of information items was extracted from each selected PSD (see Table 1). For each item, the following was extracted: (1) what was included in the sponsor's[2] submission (e.g. which comparators were proposed in the submission), (2) did the PSD cite any issues raised by the PBAC related to this item, and (3) where issues were raised, what were the particular matters of concern for the PBAC as cited in the PSD. For each of the information items, key issues were extracted and categorised into themes. Differences and similarities between drugs in how those themes emerged were explored. Extracted information was first recorded in Microsoft Word 2016 and later tabulated in Microsoft Excel 2016.

The main issues identified by the PBAC were described and summarised per variable according to the themes that emerged. Data extraction and coding was performed by YHLP and cross-checked by NvdL to ensure completeness and consistency. Discrepancies were revisited by YHLP and re-checked by NvdL to confirm their resolution.

Table 1. Key information items extracted from PSDs, and their meaning.

Variables	Meaning as defined for the purposes of this paper
Comparator	The existing health technology (or current clinical management) that will be replaced should the new health technology be implemented as proposed.
Comparison(s)	The set(s) of drugs (proposed health technology and comparator) that were compared in the analyses.

[1] According to the procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme, major submissions generally relate to requests for the listing of a new medicine or vaccine, a new indication for a currently listed medicine, or to make material changes to a currently listed indication where an economic model is required to support a claim of cost-effectiveness, cost-utility or cost-minimisation. Minor submissions generally relate to requests to change existing listings that do not change the population or cost-effectiveness of the treatment, or the listing of a new form or strength of an already-listed medicine that has a bioequivalence or equivalence statement from the Therapeutic Goods Administration.

[2] The "sponsor" of a submission can be a pharmaceutical company or another organisation or individual supporting the preparation of the submission.

Key clinical endpoints	The main outcome(s) obtained from the clinical studies, e.g. annualised relapse rate.
MCID	The smallest difference in an outcome which patients perceive as beneficial or detrimental.
Clinical claim	Assertion made by the sponsor regarding the effectiveness and/or safety of the health technology compared to its comparator (e.g. "non-inferior" or "superior").
Economic analysis	Type of economic evaluation performed (e.g. "cost-effectiveness analysis" or "cost-minimisation analysis").
Modelling	Decision-analytic modelling compares the expected costs and consequences of decision options by synthesising information from multiple sources and applying mathematical techniques.
Cycle length	Frequency with which a decision-analytic model (e.g. a Markov model) determines the costs and outcomes associated with an intervention. This impacts the precision of the model with respect to the timing of the events in number of days/weeks/months/years.
ICER	The incremental costs of the health technology compared to its comparator, divided by the incremental outcomes of the health technology compared to its comparator.
Number and types of health states	Number and types of distinct phases of a disease or treatment that are included in the decision model.
Key assumptions	Main aspects of the model that are uncertain and influence the results.
RSA	Any arrangement suggested to adequately manage risks (i.e. uncertainty in overall cost to PBS/RPBS, cost-effectiveness, or extent of overall gain in health outcomes) by sharing these risks between the sponsor and the Australian Government.
Financial impact	Projected utilisation and annual cost to the Australian Government.
Outcome of submission	Recommended, rejected or deferred.

Abbreviations: ICER, incremental cost-effectiveness ratio; MCID, minimal clinically important difference; PBS, Pharmaceutical Benefits Scheme; PSD, public summary document; RPBS, Repatriation Pharmaceutical Benefits Scheme; RSA, risk-sharing arrangement.

3. Results

Since 2006, a total of 23 submissions, covering 13 drugs, were considered by the PBAC for the treatment of MS in Australia. Seventeen submissions sought listing (or changes to the listing) for treatment of RRMS. Six submissions sought listings in other MS settings; one (glatiramer acetate) for the treatment of patients with a demyelinating event indicative of MS, one for primary progressive MS, and one submission (interferon beta – 1b) requested a review of the eligibility criteria of drugs for the treatment of MS to allow for the use of the McDonald criteria as opposed to the Poser criteria to determine patient eligibility to access treatment. Three submissions sought listing for MS-related symptoms: one (nabiximols) for the treatment of moderate to severe spasticity due to MS, and two (both for fampridine) for the symptomatic improvement of walking ability in ambulatory MS patients.

Figure 1 shows a timeline for the consideration of MS drugs over the last eleven years. Before 2006, the PBAC had already funded access to three beta-interferons (Avonex, Betaferon and Rebif) and to daily injections of Copaxone. From 2006 onwards, eight more drugs were recommended for listing. Thirteen submissions were rejected; for two drugs (fingolimod and daclizumab), the decision was deferred. The resulting approval rates were 35% per submission and 62% per drug. The mean number of submissions per drug was 1.8. Teriflunomide had the highest number of submissions (n=3).

Approval rates were higher for disease modifying treatments (DMTs) than for other drugs. For the latter, none of the three submissions (one for nabiximols, two for fampridine) resulted in a recommendation for reimbursement: a 0% approval rate. For the DMTs, approval rates were 40% per submission and 73% per drug.

While daclizumab was considered by the PBAC (July and November 2016), marketing authorisation for this product was recently withdrawn worldwide, following safety issues [10]. Cladribine, previously approved for marketing in Australia but rejected for reimbursement in March 2011, has been subsequently withdrawn. Recently, it has been reintroduced but was rejected for reimbursement in November 2017 [11].

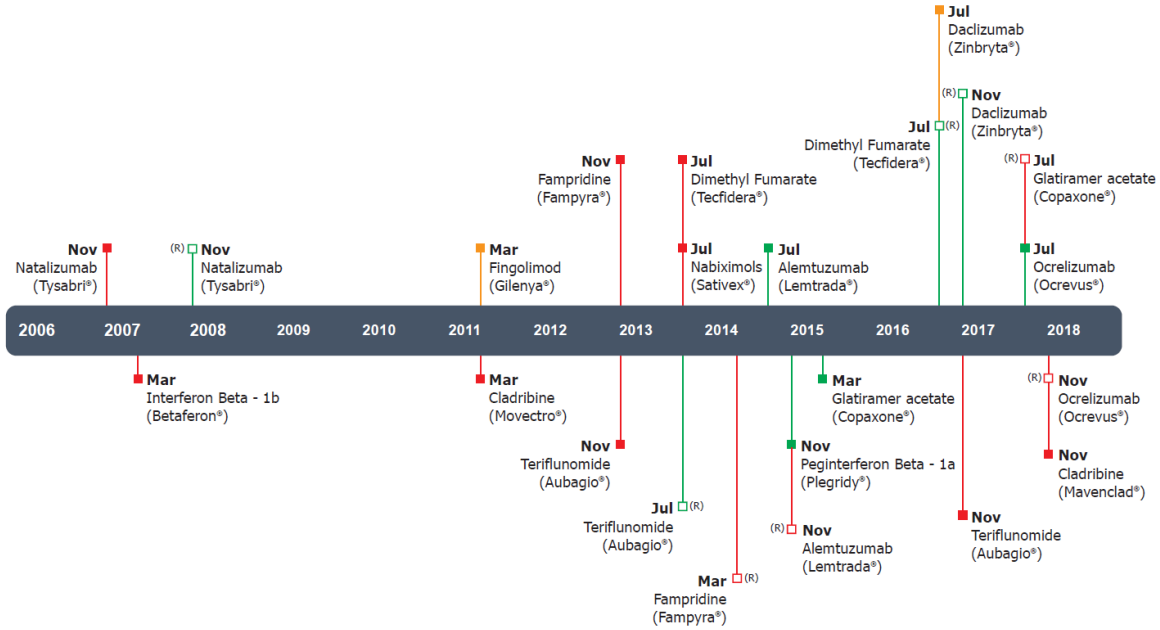

Figure 1. Multiple sclerosis drugs considered by the PBAC since 2006, and outcome of their evaluation (green = recommended, yellow = deferred, red = rejected). Open boxes with an (R) signify that this was not the first time a submission for this drug was considered.

In the PSDs of 22 of 23 submissions, the PBAC indicated issues with one or more of the following: the main comparator, secondary comparator(s), type of studies performed, key endpoints, the MCID, the clinical claim with respect to effectiveness and safety, the economic evaluation, the estimated ICER, number and type of health states, key data used, the proposed risk-sharing agreement and/or the financial estimations. For one submission (glatiramer acetate, March 2015), no issues were identified in the PSD. This was a minor submission requesting listing for an additional strength of the drug.

The issues raised by the PBAC were categorised and four themes of common clinical and economic issues emerged: the validity of the indirect comparison, the validity of the approach used to determine quality of life (including the claim that disutility is associated with injectable drugs), the lack of appropriate safety data and the time horizon used in the economic model. Each of these themes is discussed below.

3.1. Indirect comparisons

The PBAC addressed issues regarding the validity of the indirect comparison in eleven submissions: two for natalizumab (November 2006 and November 2007), one for fingolimod (March 2011), two for cladribine (March 2011 and July 2017), one for dimethyl fumarate (July 2013), two for teriflunomide (November 2012 and July 2013), two for daclizumab (July and November 2016), and one for ocrelizumab (July 2017). The issues raised by the PBAC regarding indirect comparisons can be further categorised into two sub-themes: the comparability of the trials used to inform the comparison; and the basis for claims of non-inferiority derived from those comparisons.

In the respective PSDs, the PBAC highlighted the differences between the study populations in the trials used for the indirect treatment comparisons as the major source of validity issues of those indirect comparisons. In the absence of a head-to-head randomised study, an indirect comparison can be made to compare an intervention and comparator(s). The validity of an indirect comparison depends on the similarity of the study populations in the included trials [12].

The November 2006 PSD for natalizumab indicated that the patients recruited in the trials informing the indirect comparison were insufficiently comparable at baseline, given that the annualised relapse rate at one year in the placebo group of the interferon trial was around double the risk in the placebo group of the AFFIRM trial (the key trial for natalizumab). The PSD for cladribine (March 2011) also noted the difference in annualised relapse

rate reported in the placebo arms of the trials (0.33 in CLARITY versus 1.28 in PRISMS). Similarly, for teriflunomide, the PBAC noted that the placebo response rates varied between the trials, and that there were differences in selection criteria and baseline clinical characteristics. Differences in results for placebo treatment groups between trials were also mentioned as an issue for daclizumab (July and November 2016) and a wide range of exchangeability issues [13] were listed. Exchangeability issues also hampered interpretation of results for ocrelizumab (July 2017) and fingolimod (July 2011). For the submission on dimethyl fumarate, the PBAC found the indirect comparison difficult to interpret given that two different drugs (glatiramer acetate and interferon beta-1a) were being used as the "common" comparator.

Typically, results from indirect comparisons within submissions to the PBAC are used to support claims of non-inferiority: that the proposed drug is no worse than its comparator. This was an issue mentioned by the PBAC in its review of cladribine where the PBAC noted the lack of justification for the method to calculate the minimum clinically important difference (MCID) used to assess non-inferiority. Similarly, in the first PSD for daclizumab (July 2016) the PBAC noted that a non-inferiority margin was not proposed in the submission and that non-inferiority was claimed based on lack of a statistically significant difference.

The PBAC did not always reject the results of indirect comparisons. For example, in the case of peginterferon beta-1A, the PBAC noted that the indirect comparison was appropriate given similar placebo event rates in both trials.

3.2. Quality of life

Another issue mentioned by the PBAC was the approach to quality of life adjustments used for quality-adjusted life year (QALY) estimation. This was noted in six PSDs: for four DMTs (natalizumab in November 2006, fingolimod in March 2011, cladribine in March 2011 and glatiramer in July 2017), and for both other drugs (fampridine in November 2012 and nabiximols in July 2013). Issues regarding quality of life included how utility values were obtained, and their application in the economic evaluation.

In the submission for fampridine in 2012, the PBAC noted the base case ICER of $15,000 -$45,000 was most sensitive to the choice of utilities. Utilities were noted to be highly uncertain due to a range of calculations to base changes in utilities on changes in walking speed. This mapping exercise was indicated by PBAC to be "insufficiently reliable and highly variable". The PBAC noted that there is no linear relationship between walking speed and utility, and that walking speed cannot be used as a proxy measure of quality of life. In the PSD for nabiximols (July 2013), the PBAC noted that disutilities of adverse events were not accounted for in the model, and utility values were used for three different strata of severity while there was no statistically significant difference between two of these strata.

In the submission for natalizumab, utilities derived from Fisk et al. [14] were manipulated to allow their use in the economic model, but the approach could not be verified. In the PSD for fingolimod (March 2011), the PBAC noted that when a different source of utility values was used in the model, the ICER increased substantially.

Regarding the application of utility values, the PSD for fingolimod (March 2011) discussed that the model used in the economic evaluation assumed a disutility associated with the need for frequent injections in case of treatment with existing DMTs. The ICER presented in the model was highly sensitive to this assumption. When disutility associated with injectable DMTs was removed from the economic model, the ICER increased from $45,000-$75,000 to $75,000-$105,000 per QALY gained. Assumed disutilities associated with the mode of administration were also addressed by the PBAC in the PSD for cladribine (March 2011). The PBAC did not think it feasible that the utility decrement associated with mode of administration would be approximately equivalent to the difference in utility applied for patients in EDSS 0 and 2 and greater than many utility differences between adjacent EDSS scores. In the PSD, it was not reported how sensitive the model results were to this assumption. In the model for glatiramer (July 2017), most of the health benefits were derived via quality of life improvements based on EDSS score progressions. The PBAC indicated that this lacked face validity given that a statistical difference in EDSS was not observed in the trial.

3.3. Safety data

Another main issue identified by the PBAC was the lack of appropriate safety data, arising in the PSDs for cladribine (March 2011 and November 2017), peginterferon beta-1a (November 2014), alemtuzumab (July 2014), teriflunomide (November 2012), daclizumab (July and November 2016) and ocrelizumab (July 2017).

For cladribine, the PBAC noted that there were insufficient data to accurately assess the claim of non-inferior safety, and also referred to safety findings from the TGA, FDA (Food and Drug Administration) and CHMP (European Medicines Agency's Committee for Medicinal for Human Use). In the PSD for alemtuzumab (July 2014), the PBAC noted that there were no adequate data provided in the submission to support any claim of comparative safety to fingolimod or natalizumab. In the PSDs for ocrelizumab the PBAC also rejected the safety claims due to insufficient evidence.

For various MS drugs, PSDs indicated a lack of longer term safety data. A lack of long-term safety data was mentioned for daclizumab, teriflunomide and peginterferon beta-1a. For the latter, the PBAC noted that longer term safety data beyond the 2-years reported in the submission were not available while MS treatment can span decades. Despite this issue, the PBAC indicated that the claim of non-inferior comparative safety of peginterferon beta-1a to interferon beta-1a was reasonable.

3.4. Time horizon

The last main issue addressed by the PBAC was the time horizon used in the economic models, arising in the submissions for fingolimod (March 2011), glatiramer (July 2017) and fampridine (November 2012). In the case of fingolimod (March 2011), the time horizon of the model was life-time, meaning that in the analyses patients were followed until death. Results were highly sensitive to changes in the model time horizon. When the model duration was reduced from 62 years to 5 years, it was found that the incremental cost per QALY gained increased to a range of $105,000 - $200,000 (in comparison to a base case incremental cost per QALY gained of $45,000 - $75,000). Results using a life-time horizon can be highly uncertain, due to uncertainty regarding the durability of treatment effects and differences between trial arms. Similarly, the glatiramer submission (July 2017) extrapolated to an 80-year time horizon from 3 years of trial data. The PBAC indicated that this time horizon was likely to overestimate the net effect of early treatment.

In the submission for fampridine (November 2012), the time horizon of the model was 5 years, with walking speed extrapolated from ≤14 weeks observed within the trial to a 5-year time horizon. The PBAC indicated that this was highly uncertain and noted that it potentially overestimated the treatment benefits of fampridine.

4. Discussion

This paper discussed key issues identified in PSDs regarding the Australian reimbursement of drugs indicated for MS. A key issue repeatedly identified by the PBAC as problematic in MS drug submissions relates to the validity of indirect comparisons; this issue was raised in eleven submissions. Differences between the study populations in clinical trials used for indirect comparison meant that the results were generally noted to be invalid. Another key issue for the PBAC was the validity of the approach used to obtain utilities, which was questioned in six PSDs. The PBAC noted that the utilities assumed in the model were inappropriately justified or not verifiable. Furthermore, safety issues were repeatedly noted by the PBAC: eight MS drug submissions lacked appropriate or long-term safety data beyond two years. Lastly, issues related to the time horizon used in the economic model were noted in three PSDs. These submissions were problematic in terms of extrapolation of results beyond the trial duration.

While this study focused on the Australian reimbursement process, decision-makers in different countries have been known to make different decisions regarding the reimbursement of MS drugs. Also, decision makers can set special requirements for funding, or choose to implement managed entry or risk sharing arrangements. For example, in 2002, the UK NICE concluded that interferon beta and glatiramer acetate would be cost effective for MS only if the short-term disability benefits reported in clinical trials were maintained, and established a risk sharing scheme to assess whether disability progression was consistent with a cost-effectiveness target of £36 000 per QALY projected over 20 years [15]. Interferon beta and glatiramer acetate were only recently approved for funding through the NHS, after price cuts [16].

Recent literature suggests that stakeholders are uncertain about key issues which have resulted in heterogeneous reimbursement policies and varying levels of MS drug uptake (particularly for biosimilars) between different markets [17]. The current study relied on the evidence provided in PSDs. While PSDs aim to provide a comprehensive overview of the submission, its evaluation and the reimbursement decision, they may not address all issues that were discussed by the PBAC. More information on evaluation reports and correspondence between the sponsor, the department of health, and the PBAC could have provided additional insights into issues PBAC identified and discussed.

Given that PSDs are publicly available, various authors have depended on them to analyse Australian reimbursement decisions. For example, Ngo [18] used PSDs to examine the likelihood of reimbursement given a drug's ICER. Chim et al. [7] and Wonder & Chin [19] examined whether drugs for certain types of conditions (cancer and orphan diseases, respectively) are more or less likely to receive a positive reimbursement decision than other drugs. These studies found that while PBAC is not bound by any absolute decision rule, it is possible to identify factors which increase the probability of being accepted for reimbursement.

Similar to the current study, Wonder and Dunlop [4] used PSDs to identify problems related to the quality of the clinical evidence in submissions to the PBAC. They did not perform a detailed analysis of the issues in one disease area (like MS) but performed a more general analysis of all submissions considered by the PBAC between 2005 and 2012. Their results corroborate our MS specific findings - that the clinical evidence used in submissions was "rather poor fit for purpose" [4]. According to Wonder and Dunlop, one in every two submissions to the PBAC had a significant problem with the supporting clinical evidence. The type of problems were not reported on in depth, so it is not possible to determine to what extent the specific issues discussed in our article were common in disease areas other than MS.

Given that the PBAC has repeatedly identified the same issues in MS drug submissions, more attention by drug developers and/or clinical trialists to these issues for MS drugs is required. Learning from published experience with other drugs indicated for MS, sponsors can limit the potential for rejection by providing the required information ahead of time. Some problems might be prevented at the trial development stage, by choosing the right comparator and measuring the right outcomes (incl. quality of life, adverse effects, etc.) over the right period of time. The current article can be used to inform these choices for the Australian situation. However, it is recognised that Australia is only a small part of the global market for pharmaceuticals, and Australian reimbursement requirements may not be key in determining global clinical trial protocols.

In many countries, full access and reimbursement of MS treatments is far from achieved and prevents patients benefiting from the remarkable progress that has been made in MS drugs [20]. Improved design and use of clinical studies and economic evaluations may partially alleviate these issues and might result in higher approval rates for reimbursement.

Acknowledgements
The authors thank Alexander John Waber for developing the timeline (Figure 1).

Contributors
NvdL, RDAL and MH provided intellectual leadership; YHLP and NvdL designed the research; YHLP conducted the analyses and NvdL cross-checked consistency of the analyses; YHLP wrote the paper; NvdL, RDAL and MH reviewed and revised the paper.

References

1. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies; 2014. Elsevier. pp. 225-240.
2. Palmer AJ, Colman S, O'Leary B, Taylor BV, Simmons RD (2013) The economic impact of multiple sclerosis in Australia in 2010. Multiple Sclerosis Journal 19: 1640-1646.
3. DUSC (2015) Multiple sclerosis: predicted versus actual analysis.
4. Wonder M, Dunlop S (2015) Assessment of the quality of the clinical evidence in submissions to the Australian Pharmaceutical Benefits Advisory Committee: fit for purpose? Value in Health 18: 467-476.
5. Henry DA, Hill SR, Harris A (2005) Drug prices and value for money: the Australian Pharmaceutical Benefits Scheme. Jama 294: 2630-2632.
6. DoH (2017) About Health Technology Assessment.
7. Chim L, Kelly PJ, Salkeld G, Stockler MR (2010) Are cancer drugs less likely to be recommended for listing by the Pharmaceutical Benefits Advisory Committee in Australia? Pharmacoeconomics 28: 463-475.
8. DoH (2017) Public Summary Documents Explained.
9. Rieckmann P, Centonze D, Elovaara I, Giovannoni G, Havrdová E, et al. (2018) Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: a combined perspective from the MS in the 21st Century Steering Group. Multiple Sclerosis and Related Disorders 19: 153-160.
10. MS_Research_Australia (2017) Relapsing MS treatment cladribine on the comeback (15 September, 2017).
11. Biogen (2018) Biogen and AbbVie announce the voluntary worldwide withdrawal of marketing authorizations for ZINBRYTA (daclizumab) for Relapsing Multiple Sclerosis (2 March, 2018).
12. Song F, Loke YK, Walsh T, Glenny A-M, Eastwood AJ, et al. (2009) Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. Bmj 338: b1147.
13. Alemayehu D (2011) Assessing exchangeability in indirect and mixed treatment comparisons. Comparative Effectiveness Research 1: 51-55.
14. Fisk J, Brown M, Sketris I, Metz L, Murray T, et al. (2005) A comparison of health utility measures for the evaluation of multiple sclerosis treatments. Journal of Neurology, Neurosurgery & Psychiatry 76: 58-63.
15. Palace J, Duddy M, Bregenzer T, Lawton M, Zhu F, Boggild M, Piske B, Robertson NP, Oger J, Tremlett H, Tilling K, Ben-Shlomo Y (2015) Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. The Lancer 14 (5): 497-505.
16. National Institute for Health and Care Excellence (2018) NICE approves multiple sclerosis drugs after prices are reduced, https://www.nice.org.uk/news/article/nice-approves-multiple-sclerosis-drugs-after-prices-are-reduced, accessed on 2306/2018.
17. Gran-Ruaz S, Mani A, O'Quinn S (2017) An overview of biosimilars and non-biologic complex drugs in Europe, the United States, and Canada and their relevance to multiple sclerosis. Multiple Sclerosis Journal 23: 1824-1829.
18. Ngo P (2014) The influence of cost-effectiveness evaluations on reimbursement in Australia: a retrospective study of decisions made by the Pharmaceutical Benefits Advisory Committee. Pharmaceutical Medicine 28: 187-193.
19. Wonder M, Chin G (2015) What impact does 'conventional'economic evaluation have on patient access to new orphan medicines? A comparative study of their reimbursement in Australia (2005–2012). Expert review of pharmacoeconomics & outcomes research 15: 843-850.
20. Comi G, Radaelli M, Sørensen PS (2017) Evolving concepts in the treatment of relapsing multiple sclerosis. The Lancet 389: 1347-1356.