MSTAC and Neurological Subcommittee
C/o- Andrew Oliver
PHARMAC
PO Box 10-254
Wellington 6143

1st June 2018

Dear Sirs,

Background to Submission

On Monday 28th May members of Multiple Sclerosis New Zealand (MSNZ) along with our invited guest Professor Helmut Butzkueven, of Monash University in Melbourne, met with members of PHARMAC. Following this meeting we are submitting the following letter for review along with Professor Butzkueven's presentation to further support our requests to widen the starting and stopping criteria for MS disease modifying treatments (DMTs).

For your reference, and to understand our reasoning for bringing his professional opinion into the discussion, Professor Helmut Butzkueven is currently:

- Professor and Chair of MS and Neuro-Immunology Research at Monash University
- Managing Director, MS Base Foundation
- Director, MS and Neuro-Immunology Services, Alfred and Box Hill Hospitals, Australia
- Lead contributor to MS Brain Health

Professor Butzkueven is well known and respected within the MS clinical and research circles internationally. He has worked with several NZ neurologists over the years and is highly regarded in their opinions. This submission has been prepared in collaboration with Professor Butzkueven.

This submission and its recommendations are fully endorsed by MS Specialist Neurologist Dr Deborah Mason, Canterbury District Health Board. She is willing to discuss her support of these recommendations with you.

Following our July 2017 submission, we have chosen to concentrate on the two areas we understand, from research evidence that the most impact will be achieved;

- Stopping Criteria
    a. expanding the stopping criteria to EDSS 6.0 or 6.5
    b. removing the gradient scale
- Starting Criteria
    a. removing the starting criteria of EDSS 0-4
    b. widening the starting criteria to change the requirement of needing a second relapse AND new MRI activity to be OR.

Overview of Submission

The primary intent of the current criteria is evidently to restrict access to DMT to patients who:

1) have not transitioned from RRMS to secondary progressive MS, which is not modifiable with current approved DMTs (stopping criteria);
2) definitely have RRMS rather than a clinically isolated syndrome, which may not progress to RRMS (starting criteria), avoiding misdiagnosis and inappropriate treatment for patients who do not have MS at all, but another disease such as migraine with some white matter lesions on MRI and fleeting sensory symptoms (starting criteria).

However, both the stopping and starting criteria are not based on any evidence to support them.

This submission alongside the attached presentation will present current evidence that:

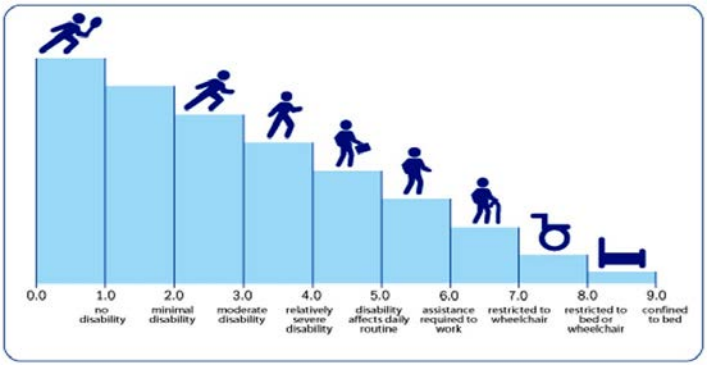
1) disputes the stopping criteria, on the basis of:
    a. 6-month confirmed disability progression events not being indicative of SPMS or treatment failure;
    b. evidence to support DMTs being effective for people with RRMS beyond the current two step deterioration on the EDSS scale up to 6.5
2) demonstrates current starting criteria are too restrictive and not in line with modern diagnostic criteria.

Stopping Criteria for DMTs

The current stopping criteria:

Stopping Criteria
Any of the following:

1) Confirmed progression of disability that is sustained for six months. Progression of disability is defined as progress by any of the following EDDSS points:
    a) from starting at EDSS 0 increasing to (i.e. stopping on reaching) EDSS 3.0; or
    b) 1.0 to 3.0; or
    c) 1.5 to 3.5; or
    d) 2.0 to 4.0; or
    e) 2.5 to 4.5; or
    f) 3.0 to 4.5; or
    g) 3.5 to 4.5; or
    h) 4.0 to 4.5.



Below we will highlight and provide evidence for reconsideration of the following areas in relation to the stopping criteria:

1) Sustained Progression Events
2) Sequential Progression Events
3) Treatment benefits at EDSS three or above
4) The need for a better definition for SPMS transition for DMT stopping criteria

1) Sustained Progression Events

The current stopping criteria identify sustained progression events (i.e. sustained for six months). However, these may not be permanent.

A recent analysis from the multinational Phase 4 TOP (Tysabri Observational Program, Butzkueven et al, 2014)[1] addresses the persistence of such progression events in relapsing-remitting MS patients treated and observed with Natalizumab (Tysabri) for up to 10 years.

Of 4161 patients enrolled in TOP with at least two years of treatment:

- 7.9% experienced a six-month sustained 2-point EDSS progression event;
- this persisted for 12 months in only 5.3%
- therefore, 1/3 of these events were not persistent for even 12 months after confirmation at 6 months. (Trojano et al, 2018)[2].

This shows that 2 point 6-month sustained EDSS progression will subsequently revert in 1/3 on patients on Natalizumab, which could lead to premature discontinuation of patients who have experienced reversible disability worsening under the current PHARMAC criteria.

After exclusion of 6-month 2 EDSS point worsening events that later reverted to baseline, it was evident that the remaining events were still much more likely to occur in patients who experience relapse(s) on Natalizumab than those who did not. In fact, these events were found in 9.3%percent of patients who did experience a relapse but only 5% of patients who did not.

This demonstrates that 2 point, 6-month confirmed progression events occur almost twice as frequently in association with residual relapses than in patients who experience relapse-independent worsening events, these latter group more likely due to SPMS.

Therefore, 2-point, 6-month sustained EDSS progression is not a good marker for development of SPMS.

Persistence of sustained progression events is also examined in a paper using the MSBase dataset (Kalincik et al, 2015)[3]. Here, the authors examined the long-term disability regression rates for various definitions of sustained progression, but 2-point EDSS progression events were not assessed.

[1] Efficacy and safety of natalizumab in multiple sclerosis: interim observational program results. Butzkueven H et al, on behalf of the TYSABRI Observational Program (TOP) Investigators. J Neurol Neurosurg Psychiatry. 2014; 85:1190-1197
[2] Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting: Trojano M et al,. Elsevier B.V. 2018. Multiple Sclerosis and Related Disorders 24 (2018) 11-19
[3] Defining reliable disability outcomes in multiple sclerosis. Kalincik T et al, Brain. 2015;138:3287-3298

One-point EDSS progression events were around 70% long-term persistent if they were confirmed at 3 months, and this improved marginally for 6-month confirmed events. 24-month confirmed EDSS increase had long term persistence of around 85-90%.

This adds additional data to the argument that EDSS progression events that are sustained for 6 months are not irreversible and are not a useful operational definition for SPMS emergence.

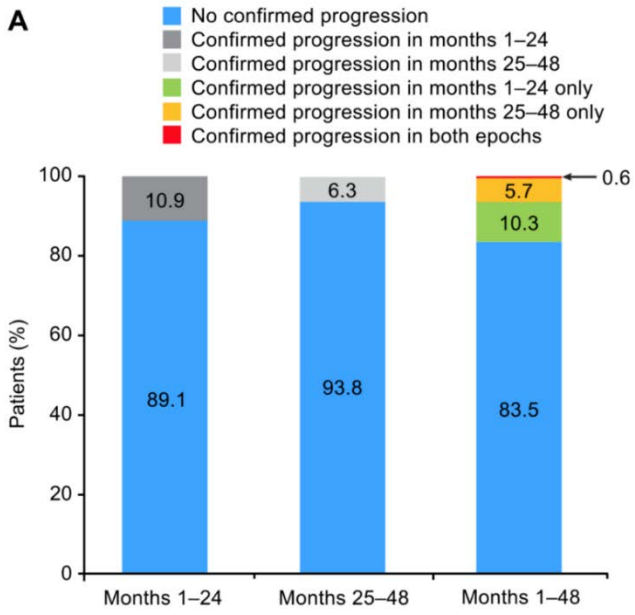
2) Sequential Progression Events

The TOP registry was also used to identify the likelihood of sequential 1-point EDSS progression events occurring in two adjacent 24-month treatment epochs in people treated with Natalizumab (Wiendl et al, 2016)[4].

The reasoning here is that if one-point EDSS progression events during Natalizumab treatment define SPMS, then it would be expected that a reasonable proportion of individuals with a 6-month confirmed EDSS progression during a 2-year treatment interval would experience a further 1-point EDSS progression in the next treatment epoch, i.e. in treatment years 3 and 4.

The graph below (from Wiendl et al, 2016)[5] shows that 10.9% of the cohort experience a 6-month confirmed EDSS progression event, but only 0.6% of the cohort experience a progression event in BOTH year 1-2 AND year 3-4.

This again adds weight to the argument that 6-month confirmed EDSS progression events are unlikely to have much diagnostic value for identification of SPMS.

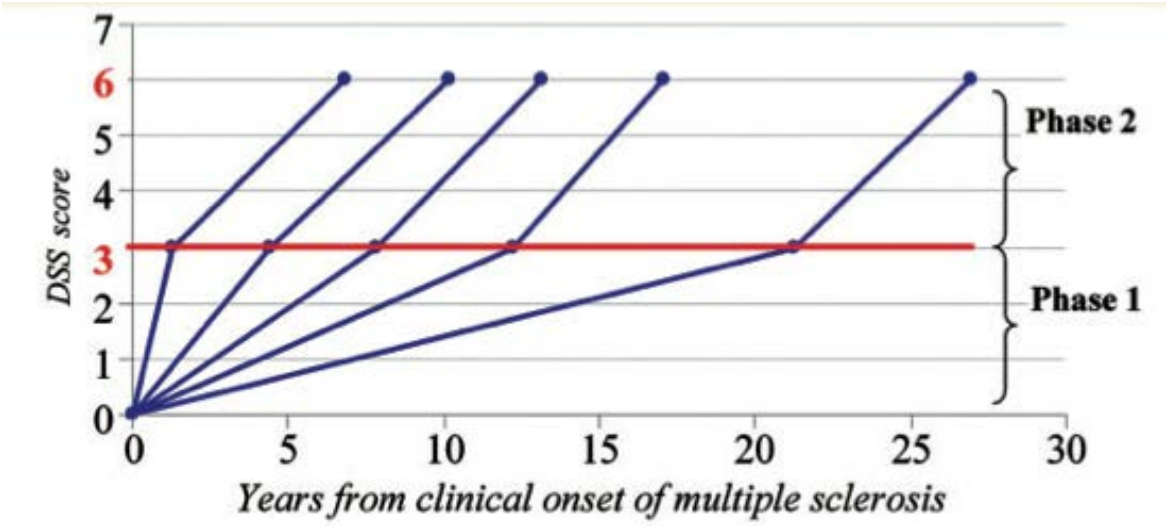


[4] Wiendl et al, Epoch Analysis of On-Treatment Disability Progression Events over Time in the Tysabri Observational Program (TOP). PLoS One. 2016;11(1):e0144834. PMID: 26771747

[5] Wiendl et al, 2016, as above

3) Treatment Benefits at EDSS 3 or Above

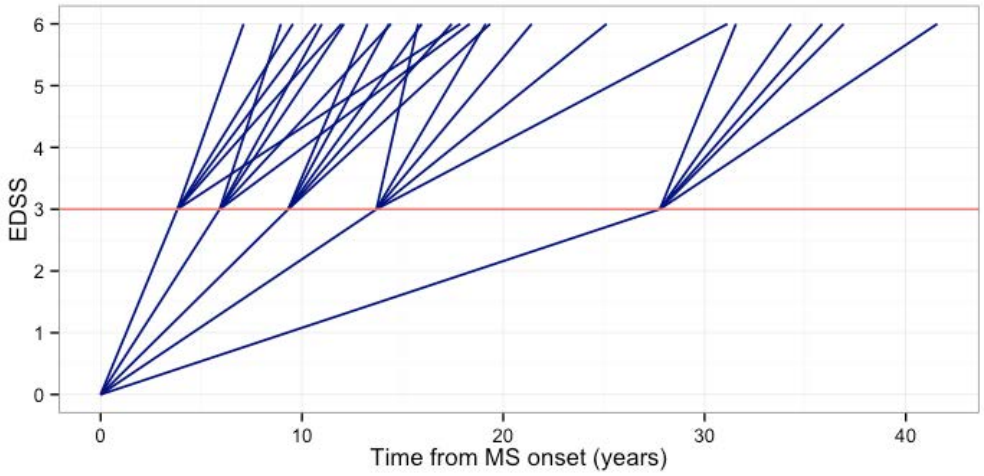
There has been a strong argument made that treatment is unlikely to help beyond EDSS 3.0. This is almost all based on the below figure, from a French cohort study, which appears to depict identical progression rates after assignation of EDSS 3 to EDSS 6. (Leray et al, 2000).[6]



While this interpretation has gained traction in the MS world, it is also incorrect.

The lower half of the figure depicts variance between 5 different groups of individuals reaching EDSS 3 at different time points, while the top half of the graph depicts the mean progression rates in these groups, and does to show the variability.

When MSBase analysts redrew the figure to show variance in both the bottom and top half of the graph, we can clearly appreciate the range of progression trajectories for individuals after EDSS 3 is in fact very broad (Lizak et al, unpublished)[7].



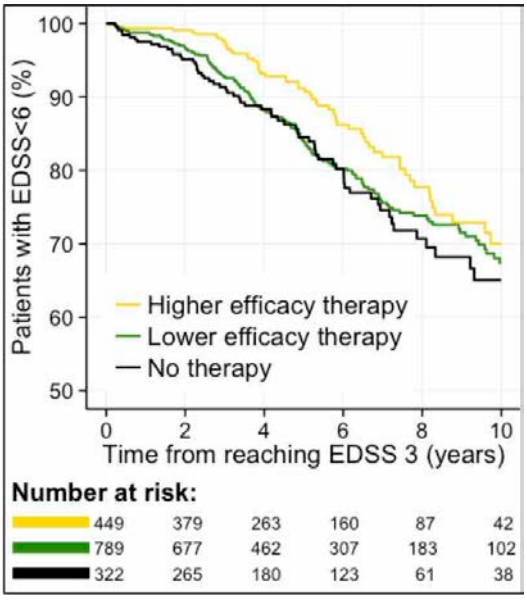
[6] Evidence for a two-stage disability progression in multiple sclerosis. Leray E et al,. Brain. 2010 Jul;133(Pt 7):1900-13. doi: 10.1093/brain/awq076. Epub 2010 Apr 27.

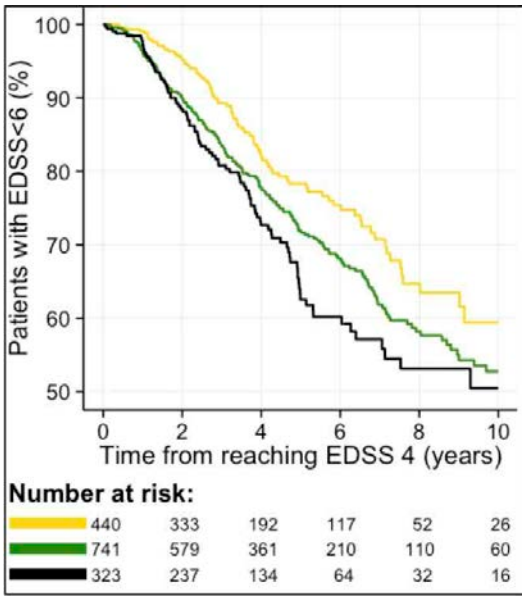
[7] (Lizak et al, unpublished) data source identical to Lizak et al, 2017

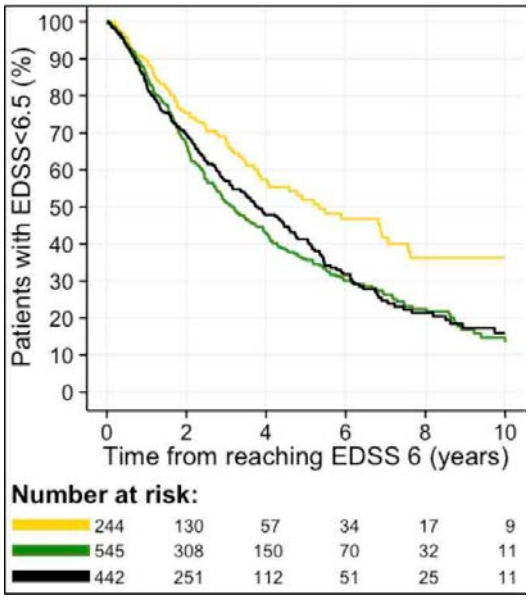
Lizak also published a paper using MSBase data to examine the effect of disease-modifying treatment in moderately severe MS, by assessing the rate of progression from confirmed assignation of:

- EDSS 3 to EDSS 6
- EDSS 4 to EDSS 6
- EDSS 6 to EDSS 6.5

The results show consistent treatment effects for high-efficacy therapy (principally natalizumab and fingolimod) in all cohorts, but greatest treatment effects for time to EDSS 6 from either EDSS 3 or 4 (see graphs below). Relapses were clearly shown in multivariable models to hasten EDSS change in all three cohorts (Lizak et al, 2017)[8].



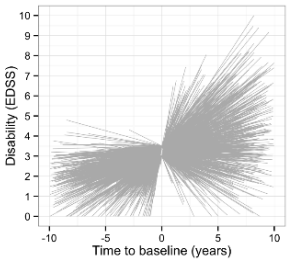


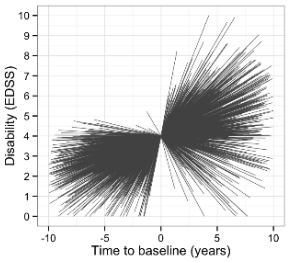


[8] Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. Lizak N et al,. Mar 2017, 2016 Sep 28. pii: jnnp-2016-313976. doi: 10.1136/jnnp-2016-313976. [Epub 2016 ahead of print] PMID: 27683916

The disease course after EDSS 3.0 has little to no relationship to the disease course up to EDSS 3.0. It also cannot be assumed that EDSS progression after EDSS 3.0 is uniform or indicated progressive MS. As you will see from the below trajectory graphs (Lizak et al, 2017)[9], at EDSS 3, 4 and 6 there is no 'one pathway' which a person's MS will take and impossible to predict. As such stopping treatment for all patients at any of these points has no evidence base. For someone who reaches 3, 4 or 6, there is potential for that individual to improve in their EDSS score or decline. The current requirement for 6 months to improve does not allow enough time for improvement to be truly visible.

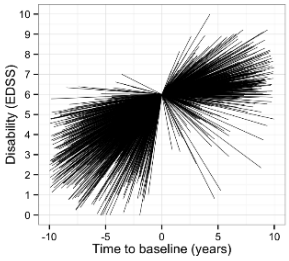
EDSS 3-6

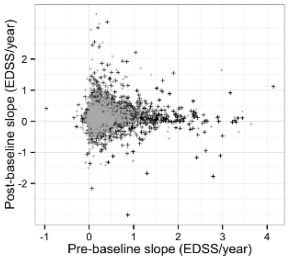




EDSS 4-6

EDSS 6-6.5





4) The need for a better definition for SPMS transition for DMT stopping criteria

Operational definitions of secondary progressive MS usually include inexorable, relapse-independent progression of walking disability for at least 12 months. Neurologists assign the SPMS classification using this definition at around EDSS 6.0.

An operational definition such as reaching EDSS 6.0 or 6.5, with inexorable progression in the absence of relapses to EDSS 6.0 or 6.5, could be implemented.

MSBase has published a significant paper describing and validating a very specific definition of SPMS (Lorscheider et al, 2016)[10].

The criteria were:

- Progression of 1 point to EDSS 4 or more, confirmed >3 months later.
- Minimum pyramidal functional score of 2 at time of progression and confirmed to be at least 2 at time of confirmation.
- Absence of a relapse in the progression period defining the EDSS change from prior EDSS to the progression EDSS of 4 or more

These criteria were found to have an accuracy of 87%, and led to a diagnosis of SPMS at an average EDSS score of 5.3. PHARMAC could also consider implementing these criteria as alternative stopping criteria.

[9] Lizak et al, as above

[10] Defining secondary progressive multiple sclerosis. Lorscheider J et al,. Brain. 2016 Sep;139(Pt 9):2395-405.

It is important at this point to clarify the difference between when a patient will have RRMS and SPMS. From a scenario perspective:

Patient A - A person with MS may have a significantly bad relapse which may move them from EDSS score 2 to 4.5 Depending on the severity of the relapse and the lesion location they may remain at this point with no further progression, or, over time with rehabilitation or allowing the lesion to reduce swelling, they may improve this score (recovery may take longer than 6 months). There is no evidence to say that even if Patient A does not improve in their EDSS score due to the lesion location that they their EDSS score will worsen further by staying on treatment. Reaching 4.5 or higher from a relapse alone does not equal conversion to SPMS.

Patient B - A person who overtime naturally progresses to EDSS 4.5 and continues to accumulate disability at a steady rate without the evidence of relapses. This person clearly has progressive MS.

Patient C - A person has a single or series of relapses reaching EDSS 4.5. Instead of either improving or having further relapses the patient continues to accumulate disability at a steady rate. This person clearly has SPMS.

5) Current Criteria's Impact on Switching Treatments

If a person with MS progresses from EDSS 1-3.5 on a treatment following a relapse and sustains this score for 6 months the current criteria will discount them from then switching to an alternative treatment which may be more suitable and beneficial to the patient. On a new and more effective treatment the persons relapses may stop and thus their EDSS stabilise in the long term. Stopping all treatments entirely is highly likely to cause further and most likely accelerated relapse-associated disability worsening for the individual. In this example, a person is denied a much better outcome of disease stability even though their disease is inflammatory (relapse-driven) and thus highly modifiable.

Summary of evidence to support review of stopping criteria

- High efficacy therapy delays progression from moderate (EDSS 3) to severe (EDSS 6) disability by up to 70% (Lizak et al, 2017)[11]
- This effect is still present in the transition from walking stick to walker (EDSS 6-6.5)- (30%) (Lizak et al, 2017)[12]
- The disease course after EDSS 3.0 has little to no relationship to the disease course up to EDSS 3.0. It cannot be assumed that EDSS progression after EDSS 3.0 is uniform or indicated progressive MS.
- A six-month confirmed progression event is not equivalent to secondary progressive MS
- It is unstable, with 1/3 of patients recovering at 12 months
- TWO "One step" 6-month confirmed progression events on NATALIZUMAB over 48 months are very rare. Almost no patients with a progression event at 24 months will have a further progression event between 24-48 months.
- EDSS progression during RRMS is not equivalent to either treatment failure OR to the development of secondary progressive MS (SPMS)

[11] Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. Lizak N et al,. Mar 2017, 2016 Sep 28. pii: jnnp-2016-313976. doi: 10.1136/jnnp-2016-313976. [Epub 2016 ahead of print] PMID: 27683916

[12] Lizak et al, as above

- EDSS progression of 2 points confirmed at 6 months is not = to permanent disability progression or to SPMS
- In RRMS, there are clear treatment benefits after EDSS 3 and up to EDSS 6.5 (Lizak et al, 2017)[13].

Starting Criteria for DMTs

Firstly, we would like to clarify that it is our understanding that there was a misinterpretation from our July 2017 submission to PTAC. It was interpreted that MSNZ was requesting access to DMTs for those with CIS and an unconfirmed diagnosis of MS. This is not the case.

MSNZ is advocating for the widening of the criteria for those who clearly have clinically defined and relapsing MS but do not fit the current starting criteria of having a second episode or relapse from the initial presenting symptoms. We agree that a person should not begin treatment until confirmation of MS has been confirmed. However, the current PHARMAC starting criteria are not in line with the international consensus as defined in the 2010 and newly revised 2017 MacDonald Criteria which accept a relapse/second episode OR new MRI activity.

The current DMT starting criteria are:

Entry Criteria

a) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
b) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
c) patients must have:
    a) EDSS score 0 - 4.0 and:
        - Experienced at least 1 significant relapse of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
        - Evidence of new inflammatory activity on an MR scan within the past 24 months, any of the following:
            i) a gadolinium enhancing lesion; or
            ii) a Diffusion Weighted Imaging positive lesion; or
            iii) a T2 lesion with associated local swelling; or
            iv) a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse; or
            v) new T2 lesions compared with a previous MR scan; and

Below we will highlight and provide evidence reconsideration of the following areas in relation to the starting criteria:

1) Removal of EDSS Score 0-4
2) Starting criteria be amended to include the acceptance of relapse activity demonstrated by clinically confirmed relapse OR new MRI activity in line with modern definition of RRMS

1) Removal of EDSS Score 0-4

MSNZ urges PHARMAC to remove EDSS Score 0-4 from these criteria as patients with relapsing remitting MS who would benefit are being denied treatment.

[13] Lizak et al, as above

An illustrative case history:

- Patient A is a female, 34-year-old, senior accountant
- She has a first episode of optic neuritis in 2017
- Followed by a second episode of transverse myelitis in 2018
- In 2017 an MRI showed 16 brain lesions
- In 2018 an MRI showed 20 brain and two spinal cord lesions
- Her myelitis initially causes leg weakness. Due to right leg weakness she needs a walking stick but recovers to be able to walk without aid or rest for 200 metres
- Diagnosis – RRMS
- Natural History Prognostic Criteria - BAD
- EDSS – 5.0
- PHARMAC – not eligible for treatment

According to the PHARMAC criteria, this patient with severe early relapsing-remitting MS would not qualify for treatment. This is akin to not allowing a patient with hypertension to be treated for hypertension because their blood pressure is too high. Please reconsider this urgently.
Please note that the pivotal trial of fingolimod versus placebo, FREEDOMS (Kappos et al, 2010)[14], had an EDSS cut-off of 5.5 for entry into the trial.

2) Starting criteria be amended to include the acceptance of relapse activity demonstrated by clinically confirmed relapse OR new MRI activity in line with modern definition of RRMS

MSNZ questions the need for demonstration of dissemination in space by both clinical and MRI criteria to qualify for DMT.

According to all modern definitions of MS, dissemination in time can be demonstrated by EITHER clinical OR MRI methods (e.g. 2010[15], 2017 McDonald criteria[16]).

Some issues to consider:

MRI access in New Zealand is limited;

- According to reports of patients and neurologists, a 6-month wait is not uncommon and currently being experienced in several DHBs across the country. MSNZ is currently submitting an OIA to DHBs for confirmation of the waiting times nationally.
- Additionally, follow up scans rarely include the use of gadolinium contrast.

However, the "evidence of new inflammatory activity" descriptors required to satisfy the PHARMAC criteria require MRI confirmation of dissemination in time include criteria such:

- as gadolinium enhancement;
- diffusion-weighted lesions;
- or enlarging lesions (lesion associated with swelling).

[14] A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. Kappos L et al,. N Engl J Med. 2010 Feb 4; 362(5):387-401. doi: 10.1056/NEJMoa0909494. Epub 2010 Jan 20.
[15] Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Polman CH1 et al,. Ann Neurol. 2011 Feb;69(2):292-302. doi: 10.1002/ana.22366.
[16] Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Thompson AJ et al,. Lancet Neurol. 2018 Feb;17(2):162-173. doi: 10.1016/S1474-4422(17)30470-2. Epub 2017 Dec 21. Review

These will NOT be present on scans performed potentially 6 months after a clinical relapse, and of course Gadolinium-enhancement can't be demonstrated if gadolinium is not given.

The requirement for a scan in the current New Zealand environment means a patient may have to wait 6 months for diagnostic first scan and then following a second clinical relapse wait a further 6 months. This has the potential to significantly delay the initiation of treatment by up to a year which is against the whole philosophy of getting patients on treatment in a timely fashion.

As such, the MS Incidence Study (Mason et al, 2017 report unpublished)[17] showed that the average age at which people developed their first symptoms was 37.8 +11.8 years. This is older than the average age recorded in previous studies. The mean age at diagnosis was 42.2 years indicating that there is a significant delay of 4.4 years between the onset of first symptoms and diagnosis. This demonstrates that people in New Zealand are missing the opportunity to be treated when it is shown to matter. The earlier that treatment is initiated the higher the likelihood of treatment success.

While the delays in MRI access are not the responsibility of PHARMAC the criteria imposed disadvantages MS patients. MSNZ will also be advocating to the Ministry of Health, Government and DHBs to address this issue with priority.

Another criterion of "new T2 lesions compared to previous scans". Unfortunately, radiologists are relatively poor at detecting new lesions, as illustrated in Dahan et al (2017)[18] where a clinical report by an expert neuro-radiologist stated new lesion detection in 10 of 76 patients, whereas software-aided detection resulted in the identification of new lesions in 34 of 76 patients.

MSNZ does not believe that application of current PHARMAC criteria is practical in the New Zealand environment with very limited access to timely MRI. We request alignment of the diagnosis of RRMS under the PHARMAC criteria to be in line with modern, internationally accepted criteria (2010, 2017 MacDonald Criteria) so that dissemination in time can be demonstrated by clinical OR radiological criteria.

A reference list has been supplied at the end of this document (Pages 13 and 14).

MSNZ hopes that PHARMAC will look favourably on this submission and that we can work together to make positive changes to benefit the lives of people with MS in New Zealand.

Your sincerely

Amanda Rose
MSNZ National Manager

[17] Multiple Sclerosis Society of New Zealand Annual Report 2016-17
[18] Computer-Aided Detection Can Bridge the Skill Gap in Multiple Sclerosis Monitoring. Dahan A et al,. J Am Coll Radiol. 2018 Jan;15(1 Pt A):93-96. doi: 10.1016/j.jacr.2017.06.030. Epub 2017 Jul 29.

Additional Note to Submission:

The New Zealand Multiple Sclerosis Research Trust and MSBase have recently formed a partnership to enhance prospective outcome evaluation in NZ MS centres, starting with centres in Christchurch and Hamilton, with strong interest also expressed by Auckland.

In this partnership, PHARMAC will be able to work with NZ neurologists to prospectively assess the impact of regulatory changes in relation to treatments prescribed, disability and relapse outcomes in NZ MS patients retrospectively and prospectively. Benchmarking against outcomes in other countries is also feasible.

Information regarding MSBase is available in the attached PowerPoint presentation along with a list of publications derived from the MSBase registry to illustrate its global position as a trusted data source.

References:

Efficacy and safety of natalizumab in multiple sclerosis: interim observational program results. **Butzkueven H**, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel R, Zhang A, Hotermans, Belachew S on behalf of the TYSABRI Observational Program (TOP) Investigators. J Neurol Neurosurg Psychiatry. 2014; 85:1190-1197.

Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting: Trojano M, **Butzkueven M**, Kappos L, Wiendl H, Spelman T, Pellegrini F, Chen Y, Dong Q, Koendgen H, Belachew S, on behalf of the Tysabri® Observational Program (TOP) Investigators. Elsevier B.V. 2018. Multiple Sclerosis and Related Disorders 24 (2018) 11-19

Defining reliable disability outcomes in multiple sclerosis. Kalincik T, Cutter G, Spelman T, Jokubaitis V, Havrdova E, Horakova D, Trojano M, Izquierdo G, Girard M, Duquette P, Prat A, Lugaresi A, Grand'Maison F, Grammond P, Hupperts R, Oreja-Guevara C, Boz C, Pucci E, Bergamaschi R, Lechner-Scott J, Alroughani R, Van Pesch V, Iuliano G, Fernandez-Bolaños R, Ramo C, Terzi M, Slee M, Spitaleri D, Verheul F, Cristiano E, Sánchez-Menoyo JL, Fiol M, Gray O, Cabrera-Gomez JA, Barnett M, **Butzkueven H**. Brain. 2015;138:3287-3298

Epoch Analysis of On-Treatment Disability Progression Events over Time in the Tysabri Observational Program (TOP). Wiendl H, **Butzkueven H**, Kappos L, Trojano M, Pellegrini F, Paes D, Zhang A, Belachew S; Tysabri® Observational Program (TOP) Investigators. PLoS One. 2016;11(1):e0144834. PMID: 26771747

Evidence for a two-stage disability progression in multiple sclerosis. Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, Edan G. Brain. 2010 Jul;133(Pt 7):1900-13. doi: 10.1093/brain/awq076. Epub 2010 Apr 27.

Lizak et al, unpublished data source identical to Lizak et al, 2017

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