Funding application for widened access to Disease Modifying Treatments (DMTs) for MS

There are specific subgroups of patients that the MS Society would like to propose widening funded access to, and these are detailed below.

1. *Clinically isolated syndrome (CIS) that fulfils the McDonald 2010 criteria for diagnosis of MS*

   The Special Authority criteria for DMTs for MS specify that a patient must have a diagnosis of Clinically Definite Multiple Sclerosis (CDMS), an Expanded Disability Status Scale (EDSS)[1] score of 0-4 and the patient must have experienced at least 1 significant relapse in the previous 12 months or 2 in the past 24 months; and must have evidence of new inflammatory activity on an MR scan within the past 24 months.

   Patients with CIS who fulfil the McDonald 2010 diagnostic criteria for MS (one attack and have MRI evidence of dissemination in time and space)[2] are not eligible for funded DMTs.

   The MS Society considers that access to funded DMTs should be widened for patients with CIS who fulfil the McDonald 2010 criteria.

   The MS Society considers that treating patients who have early MS with DMTs reduces the risk of a second attack and further disability.

   The evidence provided by the MS Society to support a benefit from DMTs for patients with CIS is as follows:

   - Giovannoni, G. et al Brain Health: Time matters in MS (2017). Available from http://www.msbrainhealth.org/perch/resources/brain-health-time-matters-in-ms-report-mar17-1.pdf
   - Proceedings of a CMSC Consensus Conference. Therapeutic Decision Making in Multiple Sclerosis: Best Practice Algorithms for the MS Care Clinician. Int. J. MS Care 16, 1–36 (2014).
   - Comi, G. et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet Lond. Engl. 374, 1503–1511 (2009).
   - Miller, D., Barkhof, F., Montalban, X., Thompson, A. & Filippi, M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. Lancet Neurol. 4, 281–288 (2005).
   - O'Riordan, J. I. et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain J. Neurol. 121, 495–503 (1998).
   - Comi, G. et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet Lond. Engl. 357, 1576–1582 (2001).

[1] Kurtzke JF. Neurology 1983;33 (11):1444–52.
[2] Table 4 of Polman et al. Ann Neurol 2011;69:292-302 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507/pdf/ana0069-0292.pdf

- Jacobs, L. D. et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N. Engl. J. Med. 343, 898–904 (2000).
- Kappos, L. et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 67, 1242–1249 (2006).
- Miller, A. E. et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 13, 977–986 (2014).
- Tintore, M., Rovira, A. & Otero-Romero, S. Factors that determine disease course: early changes contribute to predict long-term prognosis: the 'Barcelona inception cohort'. (2014).

2. *Amending the stopping criteria to EDSS 4.5 for all patients irrespective of EDSS score at entry.*

   The Special Authority criteria for DMTs require funded treatment be stopped if patients have an increasing relapse rate or if there is progression of disability by any of the following EDSS points (the first point is the EDSS at treatment entry, the second when treatment stops):

   - 0–3.0, 1.0–3.0, 1.5–3.5, 2.0–4.0, 2.5–4.5, 3.0–4.5, 3.5–4.5, 4.0–4.5

   The MS Society considers allowing for DMTs until EDSS 4.5, irrespective of the EDSS at treatment entry, reduces the risk of accumulating further disability and relapses. In addition, it considers that there may be other health benefits with regards to reduced fatigue and improved cognition by allowing treatment until EDSS 4.5.

   The evidence provided from the MS Society to support a benefit for widening access to DMTs in this group is as follows:

   - Lizak, N. et al. Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 1–8 (2016). doi:10.1136/jnnp-2016-313976
   - Hauser, S. L. et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N. Engl. J. Med. 376, 221–234 (2017).

3. *Amending the definition for 'significant relapse' in the Special Authority criteria for all MS treatments*

   The Special Authority criteria specifies that a significant relapse 'must last at least one week'.

   The MS Society considers that the definition used for a 'significant relapse' should be changed to 'must last at least 24 hours'. The MS Society considers that amending this requirement would ensure early access to DMTs to prevent disability accumulation and would align with international best practice.

   The evidence provided from the MS Society to support amending the definition for a 'significant relapse' is as follows:

- Proceedings of a CMSC Consensus Conference. Therapeutic Decision Making in Multiple Sclerosis: Best Practice Algorithms for the MS Care Clinician. Int. J. MS Care 16, 1–36 (2014).
- Polman, C. H. et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann. Neurol. 69, 292–302 (2011).

4. *Use of an alternative measurement scale to assess effectiveness of treatment.*

The Special Authority criteria for DMTs for MS utilises the EDSS as a way of measuring disability in MS to determine entry and stopping criteria for access to funded treatments. The EDSS quantifies disability in eight Functional Systems plus ambulation (mobility), with Functional System Scores in each of these functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and other. EDSS scores range from 0 to 10, in 0.5 increments. The higher the score, the higher the level of disability.

The MS Society considers DMTs for MS provide health benefits for non-physical symptoms of MS such as fatigue and cognition and that there are other disability scales available which would be more suitable than EDSS alone.

The MS Society has identified three scales, to assess effectiveness of treatment, as possible alternatives to the EDSS scale, especially beyond solely ambulation. These are the Multiple Sclerosis Functional Composite (MSFC) scale, the Multiple Sclerosis Impact Profile (MSIP) and the Performance Scales (PS).

The evidence provided from the MS Society to support a benefit of using an alternative scale to assess effectiveness of treatment is as follows:

- Fischer, J. S., Rudick, R. A., Cutter, G. R. & Reingold, S. C. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult. Scler. Houndmills Basingstoke Engl. 5, 244–250 (1999).
- Cutter, G. R. et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain J. Neurol. 122, 871–882 (1999).
- Bin Sawad, A., Seoane-Vazquez, E., Rodriguez-Monguio, R. & Turkistani, F. Evaluation of the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite as clinical endpoints in multiple sclerosis clinical trials: quantitative meta-analyses. Curr. Med. Res. Opin. 32, 1969–1974 (2016).
- Polman, C. H. & Rudick, R. A. The multiple sclerosis functional composite: a clinically meaningful measure of disability. Neurology 74 Suppl 3, S8-15 (2010).
- Wynia, K. et al. The Multiple Sclerosis impact Profile (MSIP). Development and testing psychometric properties of an ICF-based health measure. Disabil. Rehabil. 30, 261–274 (2008).
- Wynia, K., van Wijlen, A. T., Middel, B., Reijneveld, S. A. & Meilof, J. F. Change in disability profile and quality of life in multiple sclerosis patients: a five-year longitudinal study using the Multiple Sclerosis Impact Profile (MSIP). Mult. Scler. Houndmills Basingstoke Engl. 18, 654–661 (2012).
- Schwartz, C. E., Vollmer, T. & Lee, H. Reliability and validity of two self-report measures of impairment and disability for MS. North American Research Consortium on Multiple Sclerosis Outcomes Study Group. Neurology 52, 63–70 (1999).

- Schwartz, C. E. & Powell, V. E. The Performance Scales disability measure for multiple sclerosis: use and sensitivity to clinically important differences. Health Qual. Life Outcomes 15, (2017).