

2018

Clinical trials in multiple sclerosis: Milestones

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Ther Adv Neurol Disord

2018, Vol. 11: 1–7

DOI: 10.1177/
1756286418785499

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Abstract: The achievements in multiple sclerosis (MS) therapeutics are founded on the outcomes of clinical trials that demonstrate quantifiable results in treating a disease with an unpredictable course. Much has changed since the early trials in MS from the mid-20th century that compared a potential therapeutic agent with a placebo and measured outcomes based on patients' subjective reports. Advancements over the past decades have simplified diagnosis of the disease and allowed for more quantitative monitoring of its progression alongside support from paraclinical studies. Further collaborative efforts have led to pivotal meetings that steered the direction of future trials and the creation of patient databases that provided important epidemiologic information on trial subjects. These innovations and changes have improved MS clinical trials but challenge future trials to create more efficient designs lest the pace of progress necessarily slows because of the increased time to conduct such studies. As treatment options for MS broaden, clinical trials will continue to incorporate new strategies to identify novel therapies and pathways of intervention.

Keywords: multiple sclerosis, clinical trials, magnetic resonance imaging, diagnostic criteria, outcome measure

Received: 21 December 2017; revised manuscript accepted: 18 May 2018.

Introduction

Clinical trials in multiple sclerosis (MS) have led to the introduction of 15 therapeutic agents in the span of just over two decades. Prior to the modern era of these MS therapies, initial treatments of the disease during the early 20th century were empirical or experience driven and studies on potential agents were scarce and unregulated. Investigators noted many difficulties in conducting clinical trials in MS. The incomplete understanding of the disease process hindered development of therapies, and the sporadic course of MS coupled with the lack of biomarkers created difficulties in monitoring disease progression. In order to detect differences in treatments, large patient populations must be followed for long durations due to the slow evolution of clinical changes. Trials are often seen as more efficient when the population is more homogeneous. Thus, the heterogeneity of the disease excluded many patients with MS from trials due to narrow inclusion criteria. Despite these challenges, the significant achievements in MS therapies today relied directly on clinical trials that proved their

efficacy. This article reviews key events and developments that shaped the landscape of MS clinical trials.

Early studies

The first clinical trials in MS took place in the second half of the 20th century. Early trials were limited in their design due to lack of established criteria for diagnosing MS and objective measurements of disease progression. In 1961, Miller and colleagues published the results of the first double-blind clinical trial in MS studying the effects of adrenocorticotrophic hormone (ACTH) on neurological recovery during acute MS exacerbations.¹ The study enrolled 40 “consecutive patients with unequivocal MS, who presented with an assessable new symptom or sign of less than 14 days’ duration and showing no spontaneous improvement”. Subjects were matched in sex, age, disease duration, and number of exacerbations, and randomized to receive either ACTH or saline injections for their MS attacks. The authors stated that “the groups were generally

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comparable in sex-distribution, age, and duration of the disease, as well as in the proportions classified as showing initial episodes of multiple sclerosis, second or subsequent attacks during remission, or acute exacerbations of an existing disability of less than 10 years' standing". However, if one were to look critically, it is likely that the two groups were poorly matched, as it was difficult to do this sequentially with a small sample size. Results showed that ACTH improved symptoms during an exacerbation, but this was measured entirely through subjective reports from patients in a follow-up interview.

At the time, the absence of established and objective outcome measurements along with the uncertainty of characterizing relapses hindered studies from producing reliable data. The sporadic nature of the disease challenged investigators to not only find promising treatments but to devise ways to assess their efficacy. In 1969, Rose and colleagues conducted the first multicenter MS trial across 10 academic institutions in the USA.^{2,3} This was another well-controlled, randomized double-blind trial to study ACTH in the treatment of MS attacks. More importantly, the study aimed to determine whether a therapeutic agent can be reliably assessed. The investigators employed various quantitative methods to assess neurologic functions, among which was the disability status scale (DSS), that would be revised later to become the golden standard of outcome measures in MS trials.⁴ The study concluded that therapeutic agents can be objectively studied in patients with MS. Although results suggested only modest effects of ACTH in the setting of MS exacerbation, ACTH was widely employed for the treatment of MS for the next 15 years, eventually leading to high-dose intravenous methylprednisolone as a treatment for MS exacerbations.

Advancement of imaging techniques

Another major evolution over time is the growth and importance of magnetic resonance imaging (MRI) in the diagnosis of MS and monitoring of disease activity. This technology now has widespread use in clinical trials and has been central in proof-of-concept studies. Prior to the development of MRI, computerized tomography (CT) scans were unable to identify most MS lesions, and many patients with MS had normal CT scans. When contrast CT scans were first introduced to study MS lesions in 1976, enhancing

lesions could be seen and became associated with so-called active disease.⁵ These lesions also appeared to clear with steroid use.⁶ When MRI was initially utilized in studies of MS in 1981, researchers immediately noticed striking differences between MRI and CT regarding the appearance of lesions. In one of the early studies comparing the two imaging modalities among 10 patients with definite and possible MS, CT captured 19 lesions whereas MRI captured 131 lesions.⁷ MRI showed continuous activity of new lesions even in the absence of clinical symptoms, suggesting its usefulness in monitoring subclinical disease progression.⁸ In addition, imaging outcomes are more sensitive to change than clinical measures, thus requiring smaller sample size and study duration to detect treatment differences. This is especially valuable for early proof-of-concept trials but may be tied to the main focus of clinical interventions thus far in MS of reducing inflammation and the attendant consequences. The utility of other pathways of damage such as neuroprotection and/or neurorepair has yet to be shown.

In the 1990s MRI became a popular tool for providing secondary and even primary outcome measures in drug studies. In the 5-year, 1988–1993, placebo-controlled trial of interferon-beta-1b that showed a significant reduction in the frequency of MS attacks in the treatment group, MRI was used as an outcome measure and showed 80% fewer active scans and new lesion developments compared with placebo.⁹ The evidence was perhaps even more compelling biologically than the clinical data in the US Food and Drug Administration's (FDA) approval of the drug in 1993. As MRI became more widely used in clinical trials, researchers gained a better understanding of its utilities and limitations. Many MS trials have used MRI to measure disease burden and monitor disease activity.¹⁰ The use of gadolinium contrast showing enhancement of lesions indicating active blood-brain-barrier breakdown has been an important tool in confirming active MS lesions.¹¹ In addition to measuring lesions, MRI has also been used to assess unfractionated or fractionated atrophy, which corresponds to some clinical disease markers.¹² Despite these utilities, MRI lesions found on a single or annual basis have not consistently been shown to correlate with individual clinical outcomes in trials.¹³ However, Sormani and colleagues have shown that at the group level such

correlations do exist.¹⁴ Despite the radiologic utility of MRI, there is a need for improved MRI and clinical methods to characterize accurately disease states and quantify progression.

Evolution of diagnostic criteria for MS

The diagnosis of MS and classification of its disease course have important implications for clinical trial design and outcomes. MS presents with varying clinical signs and symptoms and follows unpredictable disease courses, making it difficult for trials to acquire homogeneous populations to be able to determine differences in treatment effects. Finding these so-called homogeneous groups has been a challenge. Since the first formal diagnostic criteria of MS in 1965 that introduced the principles of dissemination in space (DIS) and time (DIT),¹⁵ progress in our understanding of the disease and tools to study its clinical course have led to more accurate and simplified criteria.

Early attempts to diagnose and categorize MS focused on identifying clinical patterns of symptoms as exemplified by Charcot's triad of nystagmus, intention tremor, and scanning speech.¹⁶ Other classifications sorted patients into categories corresponding to disease course as defined by progression and relapses.^{17,18} There was a lack of unified guidelines, and diagnoses relied heavily on the clinician's intuition rather than objective guidelines. The first incorporation of the modern-day diagnostic requirement of DIS and DIT was presented in the Schumacher criteria in 1965 as a result of a committee headed by George Schumacher to develop criteria for classifying MS.¹⁵ DIS was defined as objective abnormalities in at least two central nervous system white matter locations, while DIT described their occurrence in two or more episodes lasting more than 24 hours and separated by at least 1 month or progressing over 6 months. The Schumacher criteria simplified MS trial design and allowed for objective diagnosis of clinically definite MS.¹⁵

With the development of laboratory and imaging studies to diagnose MS, Poser published criteria in 1983 that incorporated paraclinical studies such as imaging and cerebrospinal fluid (CSF) studies in the diagnosis of MS.¹⁹ The Poser criteria elaborated on the clinical classifications of the Schumacher criteria and grouped patients into

categories of definite and probable MS.²⁰ This became widely accepted as the diagnosis of MS and altered the enrollment criteria of clinical trials to accept only clinically definite and probable cases of MS.

The widespread use of MRI in the evaluation of MS led to the development of the McDonald criteria in 2001, which introduced MRI results as surrogates for the criteria of DIS and DIT.²¹ This resulted in earlier and more sensitive diagnosis.²² With its revisions in 2005²³ and 2010,²⁴ the criteria has been further simplified in which a single MRI study could fulfill the requirements of DIS and DIT. The most recent modifications in 2017 continue to facilitate the diagnosis by introducing changes where the presence of oligoclonal bands can fulfill the criteria of DIT.²⁵ In addition, requirements for DIS and DIT were further broadened to include cortical lesions and symptomatic lesions excluding the optic nerve on MRI.

The evolution of MS diagnostic criteria had significant implications for clinical trials. As diagnostic criteria became more sensitive, more patients were diagnosed earlier in the disease course. In a population of 309 patients who presented with clinically isolated syndrome (CIS) who were evaluated a year later, 16% of the cohort were diagnosed with MS under the Poser criteria compared to 44% using the McDonald criteria, suggesting patients were diagnosed earlier in their disease course under more recent criteria.²⁶ Another study showed that 50% of patients with CIS under the 2001 McDonald criteria would be diagnosed with definite MS within a year, while only 20% would under the Poser criteria. The apparently improved prognosis of CIS and MS groups is a result of the changing diagnostic criteria shifting classification of patients from higher risk groups into lower risk groups, an effect known as the Will Rogers phenomenon and/or lead time bias.²⁷ This limits comparison of historical MS populations with modern groups. Further, another concern is that when sensitivity is increased the risk of false positives (i.e. lowered specificity) can often occur. This has only been conjectured, and not formally validated.

Defining outcome measurements

In order to determine the efficacy of a potential therapeutic agent for MS, investigators were challenged with devising meaningful outcome

measurements of clinical activity. The complex clinical course of MS and the lack of biomarkers impeded the development of an objective scale to measure and track clinical changes. Prior to 1950, evaluations of therapeutic efficacy were conveyed by patients' subjective reports on whether symptoms were better, worse, or unchanged, similar in concept to modern-day patient-reported outcomes. The first attempts to develop objective scales were made by Arkin and colleagues in 1950 and Alexander in 1951.^{28,29} Alexander's approach consisted of complex scales scoring 30 neurologic signs, and proved to be cumbersome and lacked refinement. In 1955 Kurtzke developed a scale that could characterize the disability of a patient with MS and reflect changes in clinical status while maintaining simplicity.⁴ The patient was assigned a degree of disability from 0 (normal neurologic exam) to 10 (death due to MS). The DSS was first used in a study of isoniazid as therapy for MS, which was also the first multicenter, randomized, placebo-controlled, double-blind trial of a disease-modifying therapy (DMT) in patients with MS.^{4,30} The DSS was revised in 1983 to encompass more resolution with half steps rather than unitary increments and has become a universally accepted standard for measuring disability in MS.³¹

The result was the expanded disability status scale (EDSS), which has since become the most widely used outcome measure in MS trials.³² The EDSS has been used to characterize trial populations and measure objective neurologic changes in disease course. It carries the advantage of unifying clinical measurements in large multicenter trials and allowing for cross-study comparisons. MS clinicians are universally familiar with the scale and its widespread acceptance by regulators has favored its continued use in trials.^{33,34} Despite the popularity of the EDSS, it is not without flaws as the scale has been heavily criticized for high inter-rater variability, especially in the earlier steps, its disproportionate emphasis on walking, exclusion of cognitive impairment, and the scale's inherent nonlinearity.

As DMTs became available in the decades following conception of the EDSS, trials required increased sample sizes to detect differences in treatment efficacy. In 1994, a task force was formed to develop improved outcome measurements and address the shortcomings of the EDSS,³⁵ which resulted in the publication of the

MS functional composite (MSFC) in 1999.³⁶ In contrast to the neurologic examination focus of the EDSS, the MSFC was created to measure the major dimensions in which MS presents. It was designed as a clinical trial outcome measure and originally designed to capture four domains (i.e. ambulation, arm function, cognitive function, and vision); vision was excluded due to lack of data on which to base inclusion. The MSFC was required to correlate with the EDSS and assesses function in three domains including gait, upper extremity coordination, and cognition. The performance in each component is summarized using a Z-score that represents the number of standard deviations from a reference population. The Z-scores are then averaged into a single composite score providing an outcome measure on a continuous scale. The MSFC can be assessed quickly and reliably and yields more sensitive results than the EDSS and possesses predictive validity. It has also been shown to correlate better with MRI lesion burden and brain atrophy.^{37,38} Despite these advantages, the MSFC scale could not replace the EDSS as the established gold standard of measuring disability from MS. There are problems with the MSFC, some of which can be remedied, but the intuitive meaning of a composite Z-score is not easily translated into a clinically meaningful quantity. This caused the FDA to have concerns around the original use of the MSFC in the IMPACT trial,³⁹ which had major negative impacts on its adoption even though it has been used in many trials since then.

The increased efficacy of DMTs have redefined the goals of therapy, and disease activity-free status has become an attainable treatment goal.^{40,41} As more patients remain disease free with currently available DMTs, the concept of 'no evidence of disease activity' (NEDA) was proposed and adopted in 2013, drawing from the term NED used in oncology that refers to complete cancer remission without ruling out recurrence.⁴² NEDA traditionally comprises assessment of relapse rate, new or enlarged T2 or gadolinium-enhancing MRI lesions, and confirmed disability worsening. Clinicians have recognized the merit in the assessment of overall response to therapy that is not adequately captured by these individual outcome measures. The concept of NEDA as an outcome measure in MS trials has begun to see use, and the definition of NEDA continues to evolve as new components such as brain atrophy and CSF neurofilament levels are incorporated.⁴³

Currently, NEDA has not been validated in prospective studies to reflect long-term disease remission in patients at the individual level, and its wider use is limited by the inability of the composite measure to capture specific mechanisms of disease. The future of NEDA will likely adopt new imaging and fluid biomarkers into treatment monitoring, and additional experience with its use will result in a more refined and uniform definition of the concept.

Collaborations in MS trials

The achievements in MS trials are founded on collaboration among investigators, patients, pharmaceutical companies, and regulators. MS societies across different countries have provided significant support with grants and activities that fostered collaboration and advanced progress in clinical trials. Multinational organizations such as the European Committee for Treatment and Research in MS and its US counterpart the Americas Committee for Treatment and Research in MS have played influential roles in the promotion and support of MS clinical trials. These organizations were formed during an international meeting at Grand Island, NY, USA in 1982.⁴⁴ The meeting also led to the formation of the Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis of the National MS Society, which assisted in the design of future trials in the upcoming decades. The meeting represented active efforts to foster clinical trials and served as an important initial step forward for MS research and future collaborations and organizations.

Advances in information technologies have fostered the development of clinical trials and patient databases. Collaborative efforts to create databases for epidemiologic studies and clinical trials have been underway since the early part of the 20th century. The North American Registry Committee on MS in Multiple Sclerosis was created in 1996 to collect longitudinal data on patients with MS and assist with trial enrollment. Clinical trial databases such as the large-scale database from the Sylvia Lawry Center for MS research provides information on over 20,000 patients with MS. The Multiple Sclerosis Outcome Assessments Consortium placebo database provides information on placebo arms of clinical trials.⁴⁵ MSBase is the first online global MS registry created in 2004 and now contains

information on over 55,000 patients with MS.⁴⁶ It has provided important epidemiologic information and observational data on a large worldwide population with MS.

Conclusion

Clinical trials in MS advanced from developments that objectively defined and quantified the progression of a seemingly erratic disease and keen observation that a pathway focused on inflammation would lead to benefits if reduced or controlled. The introduction and refinement of MRI have led to visually quantifiable lesion loads that can be used to track radiologic evidence of disease burden and confirm periods of exacerbations. The evolving diagnostic criteria have increased diagnostic sensitivity and simplified enrollment in trials. Clinical outcome measures such as the EDSS and MSFC allow objective monitoring of disease progression. Together these milestones paved the way for significant growth in the landscape of MS trials but also created new challenges for future trials. The rapid development of DMTs in MS has led to the decreased feasibility of placebo trials due to ethical considerations and increased difficulty in detecting therapeutic effects compared with existing therapies. Fewer resources from competition among trials are demanding more efficient designs involving shorter studies and fewer patients, but these advances are limited by lack of biomarkers or surrogate outcomes. While much has been gained from clinical trials in the ongoing investigation to find the cause and cure of MS, the future of MS trials holds potentials and challenges for the setting of new milestones that must be addressed.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

YZ and AS declare no conflicts of interest in preparing this article. GC served on Data and Safety Monitoring Boards for AMO Pharmaceuticals, Biolinerx, Horizon Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva pharmaceuticals, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee); served on the Consulting or Advisory Boards for Atara Biotherapeutics, Axon,

Biogen, Biotherapeutics, Argenix, Brainstorm Cell Therapeutics, Charleston Labs Inc, Click Therapeutics, Genzyme, Genentech, GW Pharma, Klein-Buendel Incorporated, Medimmune, Medday, Novartis, Roche, Scifluor, Somahlution, Teva pharmaceuticals, TG Therapeutics, UT Houston. OS serves on the editorial boards of the Multiple Sclerosis Journal and Therapeutic Advances in Neurological Disorders; served on data monitoring committees for Pfizer and TG Therapeutics without monetary compensation; advised EMD Serono and Genzyme; currently receives grant support from Sanofi Genzyme; received travel support from Shire.

References

1. Miller H, Newell DJ and Ridley A. Multiple sclerosis. Treatment of acute exacerbations with corticotrophin (A.C.T.H.). *Lancet* 1961; 2: 1120–1122.
2. Rose AS, Kuzma JW, Kurtzke JF, *et al.* Cooperative study in the evaluation of therapy in multiple sclerosis. ACTH vs. placebo – final report. *Neurology* 1970; 20: 1–59.
3. Rose AS, Kuzma JW, Kurtzke JF, *et al.* Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs placebo in acute exacerbation. *Trans Am Neurol Assoc* 1969; 94: 126–133.
4. Kurtzke JF. A new scale for evaluating disability in multiple sclerosis. *Neurology* 1955; 5: 580–583.
5. Wulthrich R, Gigli H, Wiggli U, *et al.* CT scanning in demyelinating disease. In: Lanksch W and Kazner E (eds) *Cranial computerized tomography*. Berlin, Heidelberg: Springer, 1976, pp.239–243.
6. Vinuela FV, Fox AJ, Debrun GM, *et al.* New perspectives in computed tomography of multiple sclerosis. *AJR Am J Roentgenol* 1982; 139: 123–127.
7. Young IR, Hall AS, Pallis CA, *et al.* Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet* 1981; 2: 1063–1066.
8. Simon JH, Jacobs LD, Campion M, *et al.* Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol* 1998; 43: 79–87.
9. Paty DW and Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology* 1993; 43: 662–667.
10. Paty DW. Magnetic resonance imaging in the assessment of disease activity in multiple sclerosis. *Can J Neurol Sci* 1988; 15: 266–272.
11. Grossman RI, Gonzalez-Scarano F, Atlas SW, *et al.* Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* 1986; 161: 721–725.
12. Coulon O, Hickman SJ, Parker GJ, *et al.* Quantification of spinal cord atrophy from magnetic resonance images via a B-spline active surface model. *Magn Reson Med* 2002; 47: 1176–1185.
13. Daumer M, Neuhaus A, Morrissey S, *et al.* MRI as an outcome in multiple sclerosis clinical trials. *Neurology* 2009; 72: 705–711.
14. Sormani MP, Bonzano L, Roccatagliata L, *et al.* Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol* 2009; 65: 268–275.
15. Schumacher GA, Beebe G, Kibler RF, *et al.* Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965; 122: 552–568.
16. Guillain G. *J.-M. Charcot, 1825–1893; his life – his work*. New York: Hoeber, 1959.
17. Marburg O. Die sogenannte akute multiple sklerose (encephalomyelitis periaxialis scleroticans). *Jahrb Psychiat Neurol* 1906; 27: 213–312.
18. MacIntyre HD. Prognosis of multiple sclerosis. *Arch Neuro Psychiat* 1943; 50: 431–438.
19. Poser CM, Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13: 227–231.
20. Poser CM, Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13: 227–231.
21. McDonald WI, Compston A, Edan G, *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50: 121–127.

22. Brownlee WJ, Hardy TA, Fazekas F, *et al.* Diagnosis of multiple sclerosis: progress and challenges. *Lancet* 2017; 389: 1336–1346.
23. Polman CH, Reingold SC, Edan G, *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Ann Neurol* 2005; 58: 840–846.
24. Polman CH, Reingold SC, Banwell B, *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
25. Thompson AJ, Banwell BL, Barkhof F, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
26. Montalban X. Review of methodological issues of clinical trials in multiple sclerosis. *J Neurol Sci* 2011; 311(Suppl. 1): S35–S42.
27. Sormani MP, Tintore M, Rovaris M, *et al.* Will Rogers phenomenon in multiple sclerosis. *Ann Neurol* 2008; 64: 428–433.
28. Arkin H, Sherman IC and Weinberg SL. Tetraethylammonium chloride in the treatment of multiple sclerosis. *AMA Arch Neurol Psychiatry* 1950; 64: 536–545.
29. Alexander L. A new concept of critical steps in the course of chronic debilitating disease of the nervous system as a means of understanding response to therapy; a longitudinal study of multiple sclerosis by quantitative evaluation of neurologic involvement and disability. *Trans Am Neurol Assoc* 1951; 56: 229–231.
30. Bauer H, Thiemann KJ and Wieding E. Isoniazid treatment of multiple sclerosis. *Medizinische* 1957; 10: 33–35.
31. Meyer-Moock S, Feng YS, Maeurer M, *et al.* Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol* 2014; 14: 58.
32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
33. Cohen JA, Reingold SC, Polman CH, *et al.* Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects. *Lancet Neurol* 2012; 11: 467–476.
34. Hyland M and Rudick RA. Challenges to clinical trials in multiple sclerosis: outcome measures in the era of disease-modifying drugs. *Curr Opin Neurol* 2011; 24: 255–261.
35. Rawal N, Lee YJ, Whitaker JN, *et al.* Urinary excretion of NG-dimethylarginines in multiple sclerosis patients: preliminary observations. *J Neurol Sci* 1995; 129: 186–191.
36. Cutter GR, Baier ML, Rudick RA, *et al.* Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1999; 122(Pt 5): 871–882.
37. Kalkers NF, Bergers L, de Groot V, *et al.* Concurrent validity of the MS Functional Composite using MRI as a biological disease marker. *Neurology* 2001; 56: 215–219.
38. Becker JB, Rudick CN and Jenkins WJ. The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. *J Neurosci* 2001; 21: 3236–3241.
39. Cohen JA, Cutter GR, Fischer JS, *et al.* Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002; 59: 679–687.
40. Giovannoni G, Turner B, Gnanapavan S, *et al.* Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord* 2015; 4: 329–333.
41. Kieseier BC and Stuve O. A critical appraisal of treatment decisions in multiple sclerosis – old versus new. *Nat Rev Neurol* 2011; 7: 255–262.
42. Giovannoni G, Bermel R, Phillips T, *et al.* A brief history of NEDA. *Mult Scler Relat Disord* 2018; 20: 228–230.
43. Giovannoni G, Tomic D, Bright JR, *et al.* “No evident disease activity”: the use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler* 2017; 23: 1179–1187.
44. Multiple sclerosis. Proceedings of the International Conference on Therapeutic Trials in Multiple Sclerosis. Grand Island, NY, April 23–24, 1982. *Arch Neurol* 1983; 40: 663–710.
45. Rudick RA, Larocca N, Hudson LD, *et al.* Multiple sclerosis outcome assessments consortium: genesis and initial project plan. *Mult Scler* 2014; 20: 12–17.
46. Butzkueven H, Chapman J, Cristiano E, *et al.* MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler* 2006; 12: 769–774.