## Themed Issue of *the MS Journal*

# Advancing Trial Design in Progressive Multiple Sclerosis

# Preface

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Over the last two decades, an increasing number of disease modifying therapies have emerged that reduce relapses and relapse-related disability in patients with the relapsing-remitting form of multiple sclerosis (RRMS). Around a dozen therapies are now licensed for the treatment of RRMS in North America and Europe, with efficacy in terms of relapse rate reduction ranging from 30-75%.

In contrast to RRMS, there has been very limited progress in the development of therapies to favourably modify the course of progressive MS, whether it occurs from clinical onset (primary progressive MS [PPMS]) or after a relapsing remitting phase (secondary progressive MS [SPMS]). Indeed, it was only earlier this year that the first disease modifying therapy for PPMS gained regulatory approval in the United States, albeit with only a partial effect in slowing disease progression.[1,2] The progressive phase of MS typically leads to irreversible neurological disability often with cognitive impairment, which emphasises the pressing need to develop new and more effective treatments to substantially slow or even halt this phase of MS.

A key reason for the timely development of multiple effective therapies for RRMS was use of the new and/or active inflammatory lesion, as seen on serial magnetic resonance imaging (MRI) scans, as a primary outcome measure in relatively small and short term phase 2 clinical trials. At the study arm level, a demonstrable treatment-associated reduction in new/active MRI lesions in phase 2 trials has been followed by a treatment-associated reduction in relapse rate in subsequent larger and longer phase 3 trials[3]. Thus the pipeline from successful phase 2 to 3 trials has been expedited in RRMS.

There are multiple challenges to the development of effective disease modifying therapies for progressive MS[4]. These include a limited understanding of its pathogenesis, challenges in its clinical definition, and the high cost and logistical burden of undertaking the phase 3 trials that are required to show a reduction in the accumulation of disability. Unlike RRMS, there is, as yet, no widely accepted or robustly evidence-based surrogate measure that, when used in a short term phase 2 trial, can identify agents that will likely be shown to be clinically beneficial (in this setting that they will prevent disability progression) in phase 3. Not surprisingly, there have been many negative phase 3 trials in progressive MS.

The 2017 ECTRIMS focused workshop was held in Rome on March 9th and 10th, in association with the International Progressive MS Alliance. It was developed to create a forum for detailed consideration of strategies to improve the design of trials in progressive MS, with the ultimate aim to expedite the trial pipeline and introduce effective treatments more quickly.

The invited workshop participants covered a wide range of expertise, including neurology, neuropathology, neuroradiology, trial design, statistical, pharmaceutical, regulatory and lay viewpoints. Themes included treatment targets, trials thus far, clinical outcome measures, and interim outcome measures. The latter tended to focus on neuroprotection because

there is robust evidence that neurodegeneration (albeit due to multiple mechanisms[4,5]) is a key pathological substrate of progressive MS. In addition to MRI, for which some preliminary evidence for a treatment-responsive neuroprotective outcome measure exists[6], potential interim outcomes measures included those derived from optical coherence tomography, positron emission tomography, serum and cerebrospinal fluid (especially neurofilaments), and neurophysiology. There were also sessions that considered types of trial design, statistical analysis methodology, observations from big datasets, phase 2 trials in progress, and considerations from a pharmaceutical and regulatory perspective.

It was felt that the best way of communicating the workshop proceedings more widely would be through a Themed Issue of the *Multiple Sclerosis Journal*. In this issue, a series of papers have been assembled under the Guest Editorship of Jeremy Chataway and Robert Fox. Development of the content was assisted from notes made during the workshop by Carmen Tur and Daniel Ontaneda. Authors of the papers were also workshop participants. The papers collectively provide an account of current and emerging knowledge relevant to the design of trials in progressive MS. We hope that the information collated in this Themed Issue will be helpful in the ongoing effort to expedite effective treatments for this most disabling phase of MS.

**References**


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