Pragmatic clinical trials for treating relapsing multiple sclerosis

In his Comment,[1] Gavin Giovannoni questions the equipoise of obtaining class 1 evidence to inform early relapsing-remitting multiple sclerosis treatment via our ongoing clinical trials,[2] TREAT-MS (NCT03500328) and DELIVER-MS (NCT03535298). Giovannoni proclaims that patients with multiple sclerosis should uniformly initiate treatment with high-efficacy disease-modifying therapies (DMTs). However, there are various flaws in the evidence that he provides.

Published observational data evaluating the effect of DMTs on long-term disability have many weaknesses, the most important of which relates to the fact that DMT decisions are not random. For example, MSBase, a cohort that Giovannoni suggests provides "definitive" evidence supporting high-efficacy DMTs, does not include MRI data or the rationale for DMT choices.[3] Propensity scores do not fully relieve residual confounding in such cohorts.[4] The best way to prevent confounding by indication is through randomised trials.

Additionally, the data from phase 3 clinical trials are from trials that enroll patients with more severe disease activity and a higher overall burden than expected in this population. Furthermore, some of the trials cited included non-treatment-naive participants and did not make provisions for switching to DMTs at first evidence of breakthrough disease, as is consistent with modern practice.[5,6] TREAT-MS and DELIVER-MS do allow early treatment switches, perhaps indicating greater ethical integrity than many pivotal clinical trials.

Giovannoni states that "patients deserve the choice" of DMT. We agree, and good clinical practice includes obtaining participants' consent for trials. Our preparatory work showed that around 50% of patients were willing to be randomly allocated to a therapeutic class. In our experience, contrary to Giovannoni's claim, many who do not enroll cite an unwillingness to use high-efficacy therapy. In the USA, such therapies are often denied for first-line use by those paying for the treatment, who demand data on the efficacy from randomised trials. Traditional DMTs are commonly used worldwide, so prescribers and patients might also be uncertain about the evidence supporting high-efficacy DMTs as a first-line therapy. Notably, in the real world, with more patients with comorbidities and fewer support staff than in trials, clinicians might not be poised to optimise risk-mitigation strategies, thus further increasing the potential for harm. This reduced focus on safety is particularly important if we learn that the benefit of a so-called high-efficacy treatment is only marginal for preventing long-term disability.

The pragmatic, generalisable TREAT-MS and DELIVER-MS trials will provide the data that patients with multiple sclerosis need to make decisions about their first DMT. Given the potential risks of more aggressive DMTs and the doubts remaining about their relative long-term benefit, or the uniformity thereof, we assert that we are ethically obligated to people with multiple sclerosis to do these trials.

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Core outcomes for subarachnoid haemorrhage

Approximately 35% of patients with a subarachnoid haemorrhage (SAH) die within 3 months, and more than 50% of survivors make an incomplete recovery.[1] Despite reductions in morbidity and case-fatality over the past few decades, progress has stalled, and results from a series of randomised clinical trials have not managed to improve clinical practice.[1,2] One factor that might explain the neutral results of these clinical trials is the insensitivity of commonly used outcome measures. Another factor is that current tools do not consider what matters most to patients with SAH.[3,4] Moreover, the failure to use uniform or consistent