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.

EMM reports grants from Biogen and Genzyme, is site principal investigator for studies sponsored by Biogen and Sun Pharma, has received free medication for a clinical trial from Teva, and receives royalties for editorial duties from UpToDate. DO has received research support from National Multiple Sclerosis Society, National Institutes of Health, Patient Centered Outcomes Research Institute, Race to Erase Multiple Sclerosis Foundation, Genentech, Novartis, and Genzyme. He has also received consulting fees from Biogen Idec, Genentech/Roche, Genzyme, Novartis, and Merck over the past 3 years. NE reports personal fees and non-financial support from Biogen, and personal fees from Roche, Genzyme-Sanofi, Merck, and Novartis, outside the submitted work. He has received research support from Patient Centered Outcomes Research Institute. SDN has received consultant fees for scientific advisory boards from Biogen, Genentech, Celgene, and Merck Serono, and is an advisor for Gerson Lehrman Group, a clinical adjudication committee member for a medDay Pharmaceuticals clinical trial, and has received research funding from Biogen, Novartis, Genentech, National Multiple Sclerosis Society, Department of Defense, and Patient Centered Outcomes Research Institute (paid directly to the institution).

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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

See Online for appendix

***Panel:* Components of a core outcome set**

- Core outcome domains: a limited number of domains, representing measurable events, challenges, symptoms, or disease characteristics that are recommended to be reported in all trials of a specific condition or area of medicine; an example of a domain determined by consensus might be the symptom of headache
- Core outcome timeline: a process of mapping specific domains to timepoint(s) when they are most relevant to patients and other stakeholders and thus when they should ideally be measured; an example of a headache timepoint might be 6 months post-ictus
- Core outcome measurement instruments: the specific measurement instruments determined through consensus to characterise how the core outcome domains should be measured and reported; the specific instrument to assess headache at 6 months might be the HIT-6 measure[8]

outcome selection in SAH trials has hindered progress.[3]

A core outcome set is an agreed limited set of outcomes that all clinical trials in a specific area should minimally report.[5] It reduces selective reporting bias, enables multiple trials to be compared or combined, and promotes knowledge translation and uptake. A core outcome set for SAH should be distinct from that for ischaemic stroke. Patients with SAH often have loss of consciousness from temporary global ischaemia, have a different clinical course, and require markedly different management. Patients with SAH are more often female and are generally younger than those with ischaemic stroke.[1] Only limited data exist on the outcomes that are most important to SAH patients, and the most commonly used outcome measures in SAH studies were not developed specifically for SAH.

Recently, an international multidisciplinary collaboration under the auspices of the National Institute of Neurological Disorders and Stroke (NINDS), Neurocritical Care Society (NCS), and the National Library of Medicine (NLM) reported the first iteration of the Common Data Elements (CDE) project, improving standardisation in SAH research.[6,7] Through necessity and circumstance, the processes listed above have primarily included two stakeholders: researchers and health-care providers. But patients and their families should have equal importance in the process. The development of core outcomes should ensure that patients have equal representation throughout all phases, and it would therefore represent a unique consensus project with a notably more diverse group of participants.

The development of a core outcome set for SAH should be consistent with the accepted methods established by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative and the Outcome Measures in Rheumatology (OMERACT) consortium (panel). Conceptually, there should be three main components: domains (what to measure), timepoints (when to measure), and measurement instruments (how to measure).[5]

This process is necessary to address an important knowledge gap, enhance clinical trial methodology, and optimise comparison between trials. The next steps should include the report of a detailed protocol that sets out robust methods for developing consensus. Standardising outcome measures drives the translation of research into practice, leading to improvements in patient outcomes.

We declare no competing interests. This letter results from the discussions of an international group of SAH researchers, health-care providers, SAH survivors, families and foundation representatives, who were invited to a roundtable discussion about how to improve outcome measurement in SAH research that took place on June 25, 2019, in Amsterdam, Netherlands. The group reached a strong consensus regarding the need of a core outcome set specifically for SAH, and the need for involving multiple stakeholders throughout the process of its development. The roundtable was funded by an Innovation Grant administered through The Ottawa Hospital Academic Medical Organization, ON, Canada. The funders played no part in the discussions or writing or the decision to submit the letter for publication. For the members of the Subarachnoid Haemorrhage Working Group see appendix.

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