The treatment of patients with Multiple Sclerosis (MS) has been transformed over the past two decades with a rapidly expanding list of disease-modifying therapies totalling 10 in the USA and 11 elsewhere. This has made choosing a treatment more challenging for specialists and patients alike. Although direct head-to-head randomised controlled trials of all available therapeutic options would theoretically provide the best evidence base to guide patient management, we argue that this approach is impractical and fraught with difficulties; with the right tools, independent clinical trials can be used to compare the relative efficacy of treatments.

Although patients with MS are heterogeneous, presenting with a wide variety of clinical manifestations and variable degrees of disease activity and progression, there are standardised criteria to establish the diagnosis and the clinical course of the illness, and to monitor its progression. Clinical trials almost universally use the McDonald’s Criteria to confirm the diagnosis, the Lublin criteria to define the clinical course, the Expanded Disability Status Scale to assess clinical disability and standardised magnetic resonance imaging (MRI) imaging techniques to monitor disease activity and progression. This makes the patient populations studied and the outcomes used reasonably comparable. In addition, although the study design of various trials may vary from one study to the other, similar outcome measures, including relapse rates, disability progression and lesion load on imaging, are invariably reported. It is therefore possible, with the use of appropriate statistical analytical tools, to use independent trials to compare treatment efficacy.

There is a paucity of head-to-head treatment efficacy trials in MS. Those that have been conducted have created controversy rather than bring clarity. The INCOMIN trial, which compared the efficacy of interferon beta-1b (Betaseron) with intramuscular interferon beta-1a (Avonex) in relapsing–remitting MS, showed a significant difference in the percentage of those remaining relapse free in the interferon beta-1b group. A subsequent trial by a Danish group published 4 years later comparing Betaseron with another interferon beta-1a (Rebif) showed no significant difference in the annual relapse rates between the two groups.

A further head-to-head study comparing Rebif and Avonex, the EVIDENCE trial, showed that a higher percentage of patients receiving Rebif were relapse free and had fewer active lesions on MRI at 24 and 48 weeks than those on Avonex. However, there were several criticisms of this trial including the fact that it was not double-blinded and that patients were only followed up for 6 months. More recently, alemtuzumab was compared with Rebif in two phase III trials which seem to give similar results in relation to the effect of this agent on relapse rate, but different results in relation to its effect on disability progression.

These examples, and many others, highlight several issues which need to be considered. Head-to-head trials have many limitations and may not provide a definitive answer. The number of therapeutic options is rapidly expanding, and to conduct trials that would provide definitive answers requires a large number of patients taking part in a single trial with multiple therapeutic arms or a significant number of smaller trials comparing various treatment options. This is an exceptionally difficult task which requires substantial funds and the ability to follow patients up for a long period of time.

Furthermore it is extremely expensive to develop new medications and conduct clinical trials. At present, especially in the current financial climate, no government or academic institution can fulfil this need. The neurology community remains highly dependent on
the pharmaceutical industry for this. It is reported that Pharmaceutical Research and Manufacturers of America member companies have spent approximately £330 billion since 2000, which they invested in research and development including clinical trials; the bulk of these trials were placebo controlled. Shifting the paradigm towards head-to-head trials risks disengaging pharmaceutical companies from investing in new treatments and diverting resources to smaller inconclusive studies, covering only a small proportion of potential head-to-head permutations.

Network meta-analysis, which combines evidence from direct and indirect comparisons of treatments, is a well-established method that is widely accepted and used for this purpose, including the Cochrane Collaboration, when producing guidance for physicians. Using this approach and on the basis of the effectiveness data of several placebo-controlled trials, fingolimod was compared with interferon, glatiramer acetate and natalizumab and found to offer the most favourable profile in terms of relapse-free rate at the 1-year follow-up assessment.

Whilst trials are relied on to guide choice of disease-modifying treatment, patients who need such therapies may be significantly different to those included in the trials. Registries of patients with MS will prove invaluable in addressing this issue. Although several MS patient registries exist, the data collected for their databases lacks consistency at present. Setting up more registries and reaching a consensus to ensure uniformity of the data recorded worldwide may prove to be an invaluable resource for determining the true efficacy of treatments both in the short and long term, and for monitoring for adverse effects. Using a similar approach, the Risk-Sharing Scheme was established in the UK to assess the cost-effectiveness of first-line disease-modifying therapies by prospectively collecting disability-related data from treated patients and comparing the findings with a natural history cohort.

In conclusion, given the robust, widely used criteria for diagnosis, grading and measuring outcomes and the relatively large number of therapeutic options, the limited resources are best spent on well-conducted robust independent trials for therapeutic drugs in MS which can, with the right statistical tools, be compared to guide clinical decision making.

**Conflict of interest**

BS has been an investigator in clinical trials referred to in this article and has received research support paid to his institution from Biogen Idec and Merck Serono. DD declares no conflict of interest.

**References**