Editorial

Clinical trials from the past to the present

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Randomized controlled trials provide the highest level of evidence for the way we practice medicine, particularly in our choice of treatment. But the results of these trials often have limited applicability to specific patients, as participants in clinical trials are not exactly the same as the patients who show up in our clinics and hospitals. Even beyond the exclusion and inclusion criteria of clinical trials, other factors distinguish patients in our practices from those in trials. Patients in well-conducted trials are monitored closely, and the data are meticulously collected. While we all like to think we follow our patients carefully and appropriately, does this happen in real life? To address this issue Pragmatic randomized trials were devised. Pragmatic randomized controlled trials hope to make sure that money spent on RCTs is well spent by providing information that actually matters to real-world outcomes.

As teachers, we tell students to read the entire published clinical trial report, not just the abstract and conclusions. Over the years, number of journals and clinical studies published have increased exponentially. Naturally we are not in a position to read all these. Usually, the articles that I merely skim lie outside my sub subspecialty areas of interest, as time constraints make this abridged reading a necessity for survival as an academic and a specialist.

Another issue with trial data are they may be outdated. Trials done 10-20 years ago may not be valid today. Conditions of patients, selection and diagnostic criteria can be different. Life styles then and now are not comparable. Older clinical trials in epilepsy lumped all patients together, specific types of epilepsies were not distinguished but treated with the same drug. Now we know that specific syndromes respond differently to different drugs. So the older data may not be valid today. We also have newer agents targeting specific syndromes. Earlier stroke studies too suffered the same methodological issues. Now we know to distinguish embolic stroke from lacunar strokes and lumping all in one study may bias the results. Multiple sclerosis is another condition with newer drugs available for treatment.

Over the last two decades, clinical trials in MS have established a success rate of 27%, defined as passing phase I, II, III and United States Food and Drug Administration (US FDA) approval. As a result of now having 15 approved disease-modifying therapies (DMTs) for relapsing-remitting MS (RRMS), there is a greater challenge to improve the existing options and to achieve prolonged remission. The increased availability of treatment along with revisions in the diagnostic criteria have changed the clinical trial population and restricted the implementation of placebo-controlled trials. At the same time, an increased understanding of the pathophysiology and natural history of the disease have spurred the development of new outcome measurements. Despite numerous successes in advancing therapies for RRMS, similar progress has not been achieved for patients with progressive forms of MS (PMS), and previously failed trials in PMS have delineated the challenges that must be overcome to develop treatments for PMS. The design of MS trials must take its dynamic landscape into consideration and account for the differences between modern and historical trials. In later trials there is a shift from placebo-controlled trials to active comparator studies, and from traditional to new outcome measurements.

The past 25 years have witnessed substantial developments in the treatment of MS. Advancements in therapeutic agents are a direct result of clinical trials that demonstrated their efficacy. Just as the disease course has been redefined with the advent of DMTs, so have characteristics of trials that continue to test new agents. The present-day MS trial population no longer shares the same baseline characteristics as historical groups and is distinguished by earlier diagnosis and milder disease presentation due to increased availability of treatment. This change is present even in placebo groups, thus complicating the comparison of data across trials. At the same time, active comparator designs have replaced placebo-controlled trials for RRMS, as the latter is no longer ethical in an era of proven therapeutic options. The head-to-head comparison of two agents has increased the required trial sample size and duration to be able to detect significant differences.

At the same time, new options for clinical and neuroimaging outcome measurements are beginning to be used in trials to capture different aspects of the disease process. While traditional measures of relapse (e.g. changes in EDSS and focal MRI lesions) continue to remain the standard of assessment of disease activity, new parameters such as brain volume, PROs, MTR, OCT, NFL have contributed new dimensions to outcomes.

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