controlled studies for MS, only active comparator studies be performed.

First, by performing active comparator studies (noninferiority studies or superiority studies without a placebo group), the issue of the ethics of placebo-controlled studies becomes moot. Second, while it is true that something is lost by omitting placebo groups, something is gained by the use of active comparator groups and I think that what is gained outweighs what is lost.

From a statistical standpoint, it seems that patient populations recruited for a previously performed placebo-controlled study and for a planned active comparator study may not be the same, and for that reason active comparator studies are inappropriate. However, when considering which MS medication to use, for example, the great majority of clinicians base their decisions on results of published studies without considering the details of strict comparability of the patient populations in the studies.

Medical care is delivered on that basis. While placebo-controlled studies provide information as to whether a medication is effective, active comparator studies are valuable to clinicians since they provide at least some information as to whether the test medication is effective and importantly, how it compares to the EET, which is valuable information to clinicians.

The statistician may argue that something is lost because the recruited patient populations may not be the same. For example, in a planned study comparing a beta interferon—shown to be effective in a previous placebo-controlled study—and a new medication, something is lost by not performing an active comparator study. As a non-statistician, I would argue that in instances where an EET for an illness has been demonstrated in placebo-controlled studies, trials of new medications should be performed vs the EET.

Placebo-controlled studies have been the gold standard of treatment trials. But just as the United States went off the gold standard in 1933, possibly it is time to make a similar change in considering treatment trials.

Richard B. Tenser, Hershey, PA

Disclosure: The author reports no disclosures.

Reply from the Authors: We thank Dr. Tenser for his interest in our article¹ and for his comments.

We agree that active comparator studies of experimental agents against EET therapy can provide clinical guidance and can contribute to demonstrating efficacy and safety (thus benefit/risk) of a new compound in comparison to EET.

In our opinion, for active comparator studies in MS, a superiority design is preferable to a non-inferiority design, the latter of which can be an invitation to a poor quality study and requires an arbitrary choice for what is considered to be a tolerable difference for inferiority. In addition, inherent noise in measuring MS outcomes (such as Expanded Disability Status Scale) and variability in patient responsiveness to EET will tend to favor an evaluation of non-inferiority when no signal—only noise—is being detected.

However, when ethically and practically acceptable, a placebo-controlled study design is more informative and may be more efficient in terms of numbers of subjects and duration of studies. In addition, some regulatory agencies currently require a placebo arm to be included in study designs—even superiority studies—to provide a gauge of assay sensitivity of the experimental agent.

Our intent was not to promote placebo-controlled studies over their alternatives, but to provide perspective and guidance on the ethics of randomized clinical trials in MS, with a focus on placebo-controlled studies. Consideration of ethics is a necessary prerequisite for providing further and better treatment options available to patients with MS without unnecessary delays.

Chris H. Polman, Amsterdam, The Netherlands

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1. Polman CH, Reingold SC, Calabresi PA, et al. Ethics of placebo-controlled clinical trials in multiple sclerosis. *Neurology* 2008;70:1134–1140.

CORRECTION

A structural basis for reading fluency: White matter defects in a genetic brain malformation

In the article “A structural basis for reading fluency: White matter defects in a genetic brain malformation” by B.S. Chang et al. (*Neurology*® 2007;69:2146–2154), author Stephen Wong should have been listed as Wong ST. The authors regret the error.

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A structural basis for reading fluency: White matter defects in a genetic brain malformation

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