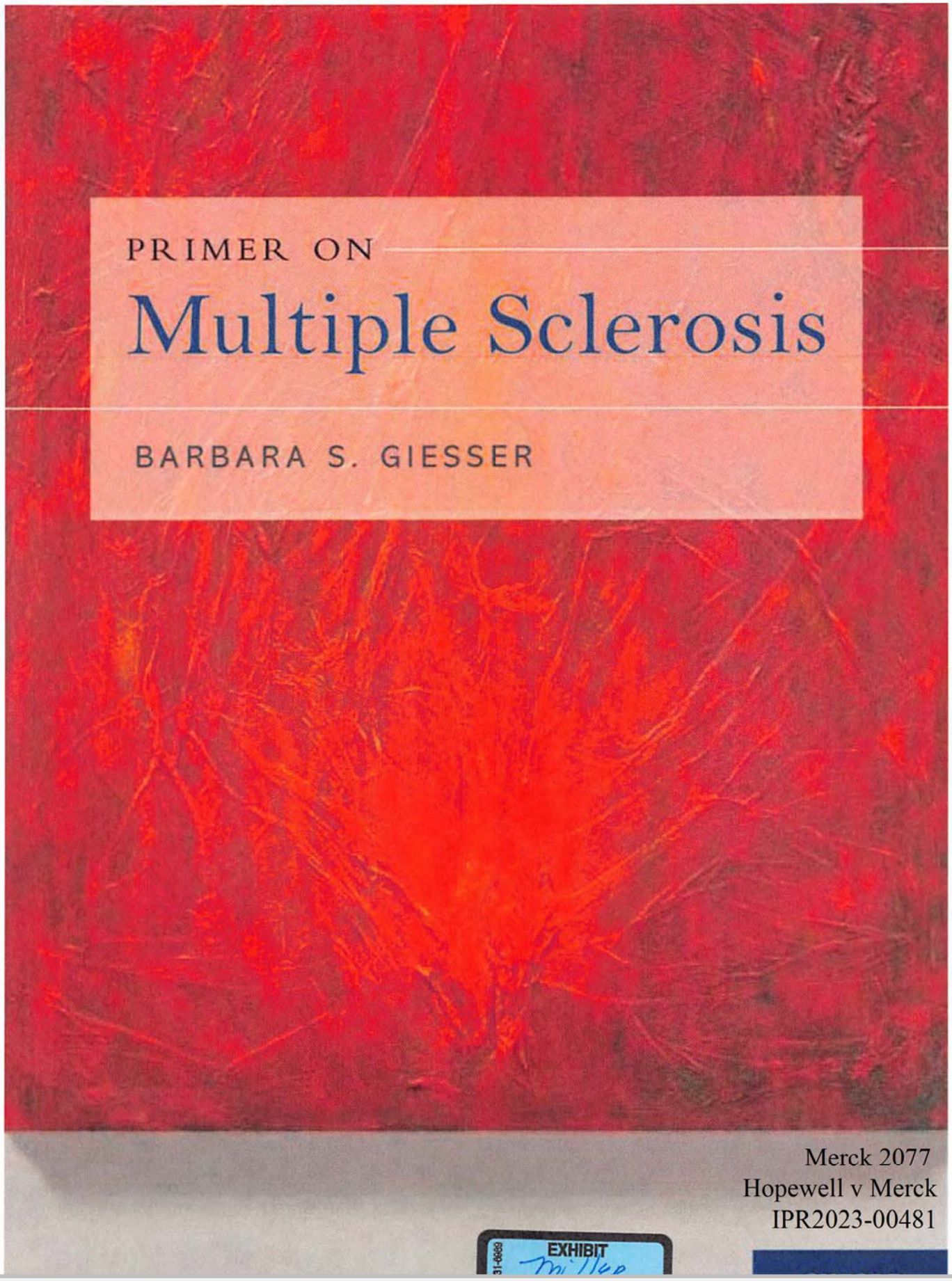

# Primer on Multiple Sclerosis

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# 29 Issues in the Design and Interpretation of Multiple Sclerosis Clinical Trials

*Stephen Krieger, Svenja Oynhausen, and Aaron Miller*

Multiple sclerosis (MS) is a disease whose heterogeneity poses unique challenges in making the diagnosis, offering prognosis, and deciding about treatment. The heterogeneity may pose even greater challenges in the design of clinical trials because it leads to problems of operational definitions, ascertainment of clinical data, and selection of meaningful outcomes as they pertain to characterizing the disease course. Applying the results of clinical trials to individual patients adds an additional degree of difficulty.

The natural history of MS has been well characterized over the past several decades. Although there are numerous methodological problems with the direct use of natural history controls, the entire enterprise of designing clinical trials for MS begins with applied natural history. Assumptions about the expected behavior of the disease are implicated in trial design, outcome selection, entrance criteria, and power calculations. Clinical trials of MS treatments are typically short term, relapse, or magnetic resonance imaging (MRI)-based studies; long-term benefits assessed utilizing robust clinical measures remain to be definitively established. As the disease course typically spans several decades, it is particularly difficult to draw firm conclusions about the consequence of treatments that have been available for only a fraction of this duration. Indeed, it is not clear how best to determine whether, and to what degree, current medications are influencing the long-term course of the disease (Noseworthy, 2007).

A discussion of MS clinical trial design and interpretation must begin with a critical review of the operational definitions used to characterize the disease. The broad range of MS disease course has been delineated into four subtypes, relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). It should be emphasized that the names for the clinical subtypes are of limited, mostly descriptive applicability. As they are based solely on the effects of the disease that cross the clinical threshold, the categories do not necessarily reflect the true underlying pathological heterogeneity. In RRMS, for instance, the formation of new T2 lesions is far more common than the occurrence of clinical attacks, indicating that even during periods of clinical quiescence, tissue damage continues to accumulate. The subtypes also vary in their definition as they apply to the temporal course of MS: PPMS is a discrete subtype, but RRMS and SPMS can both occur in the same individual at different points in his or her disease course. In addition, the transition from RRMS to SPMS is indistinct and can only be definitively identified in retrospect. One, therefore, cannot know whether a patient with RRMS has already begun to progress at the time of enrollment into an RRMS trial.

Nonetheless, these categories are most useful in the context of clinical trials, where homogenous populations are desirable to most clearly discern a therapeutic effect, and much of the successful work in the field, as well as the focus of this chapter, pertains to relapsing-remitting disease. Although necessary from a trial design perspective, the use of categories that are not biologically defined imposes several assumptions on the planning of a trial. As Randy Schapiro (personal communication) has noted, "There is no relapsing-remitting MS or secondary progressive MS—there is only MS."

While MS experts debate whether MS is one disease or many, confining clinical trials to a particular disease state not defined by distinct pathophysiologic mechanisms may increase both false-positive and false-negative results for clinical research. The reliance on these classifications for clinical trials limits the generalizability of the results across the entire MS spectrum, and it typically restricts approval and licensure of an agent to the subtype of MS in which it has been studied. An era in which the subtype-delineations are likely to be updated, as genetics and biomarkers become available to better elucidate the pathological substrates for clinical patterns, is likely beginning.

Clinical trials in MS have, since the early 1980s, followed a traditional "double-blind, placebo-controlled, randomized paradigm" (McFarland and Reingold, 2005) and have led to the approval of six agents for the treatment of MS. The widespread use of these treatments has transformed the management of MS and has significantly impacted the design of clinical trials that are needed to find safer and more effective therapies for relapsing MS and to test new therapies for other as yet untreatable forms of the disease (McFarland and Reingold, 2005). Despite the extraordinary advancements in neuroimmunology, rational drug development, and clinical trial design and analyses, clinical trials are hampered by an incomplete basic understanding of the MS disease process, the mechanism of action of the agents under investigation, and the ideal way to gauge their clinical effectiveness. The hope is that early treatment will impact long-term course and the subsequent development of disability, but there is, as yet, little convincing evidence that our current agents affect this outcome (Noseworthy, 2007). In addition, the currently available therapies are only partially effective, have side effects, are difficult to deliver, and are expensive. However, the widespread availability and clinical acceptance of these agents has led to a transformation in the design of modern MS clinical trials, one that is both ethically and practically based (McFarland and Reingold, 2005). Currently, more than ever, a dynamic pipeline of parenteral and oral agents is already in phase III testing so that several new agents may reach the market in the next few years. This new landscape of MS therapeutics presents novel challenges to future clinical trials, and this chapter will review the assumptions and design considerations of pivotal and recent MS trials to provide a historical perspective on how we have arrived at the present moment in considering the future of MS research. It will conclude with an evaluation of the current state of ethics of placebo-controlled trials, as well as an overview of new approaches to the study of MS that take a more holistic approach than that of the traditional clinical trial.

## CLINICAL TRIAL OUTCOMES MEASUREMENT: AN OVERVIEW

Multiple sclerosis clinical trials must be designed to capture the broad array of potential disease manifestations across individuals, but they must do so in a way that is reproducible and standardized. Outcome measures must be multidimensional in order to adequately encompass the myriad ways MS effects patients both in the short and long term. To this end, clinical trials focus on the two hallmark characteristics of MS: the occurrence of relapses and the accrual of disability. Choice of the outcome measure depends on the presumed mechanism of action of the investigated treatment and its anticipated clinical effect. It is important to choose the most appropriate primary outcome measure for each individual trial (D'Souza et al., 2008). In addition, a study must be of sufficient duration to allow the benefit of the agent to become evident and have a subject population large enough to power the study adequately. As long-term disability cannot be adequately assessed directly in a short-term clinical trial, all of our clinical measures from relapse-based assessments to measures of sustained disability in the short term can be considered surrogate markers of our ultimate long-term therapeutic goals.

### Short-Term, Relapse-Based Outcomes

Clinical trials of disease-modifying agents for MS typically utilize relapse-based endpoints to demonstrate therapeutic effect. As short-term trials (usually between 1 and 3 years in duration) are often underpowered to demonstrate effect on long-term disability, endpoints such as the annualized relapse rate, time to first relapse, and percent of patients relapse free serve as surrogate

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