

Accelerated Cure Project for MS

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Are Comorbidities Hindering MS Clinical Research?

As discussed in our [October 2017 newsletter](#), clinical research is the study of health and illness in people. It is the way we learn to prevent, diagnose and treat diseases. A clinical trial is one type of clinical research study. Clinical trials are most often done to determine whether new drugs, treatments or devices are safe and effective. Some studies involve healthy subjects, and others pertain to patients with specific health conditions who are willing to try an experimental treatment. Some clinical trials also look at other aspects of care, such as improving the quality of life for people with chronic illnesses, like MS. Others test ways to find a disease early, sometimes before there are symptoms, or prevent a health problem.



Every clinical trial has specific requirements for who can or cannot participate, called [inclusion and exclusion criteria](#). These prerequisites are used to protect subjects' safety during a clinical trial. Inclusion criteria, as the name implies, are those standards participants must meet in order to participate in a study. There are also factors that can bar some subjects from participating, which are exclusion criteria. In order to enroll in a clinical trial, subjects must qualify by satisfying both the inclusion and exclusion criteria. These standards are often related to a wide variety of factors, including one's age, gender, type and stage of a disease, previous or current medications or existing medical conditions.

Clinical trials can be classified in two categories – [explanatory or pragmatic](#). In general, explanatory trials test the effectiveness of a treatment in a highly selected, uniform group of subjects. Participants are selected using strict inclusion and exclusion criteria and all aspects of the study are controlled. These rigid requirements eliminate confounding factors in a study and enable researchers to take a “clean” look at the parameter of interest. However, findings from trials conducted under these “ideal conditions” may not be generalizable to the broader population. For example, if having high blood pressure excludes subjects with MS from participating in a clinical trial looking at a new MS treatment, no data will be collected on the safety and effectiveness of that treatment in people with MS and hypertension. Therefore, the results of that study may not apply to these individuals. Clinical trials in MS to date largely have been explanatory in nature. In contrast, pragmatic trials attempt to understand the real-world benefit of a treatment. This type of clinical trial has a more flexible design (for example, includes a more varied subject population) that allows for wider clinical applicability of study results.



As discussed in our [February 2018 newsletter](#), diversity is essential in clinical trials to ensure their findings benefit everyone. [Research](#) shows individuals with comorbidities, in general, are underrepresented in clinical trials. Comorbidity is a medical condition that occurs with another illness in the same person at the same time. Therefore, the results of these studies may not apply to a typical population with coexisting diseases. The [MS Comorbidities Project](#) (MSCP) characterized the types and frequencies of comorbidities in MS and other diseases, as well as their [prevalence in clinical trials](#). Researchers reviewed studies on diabetes, heart failure, chronic obstructive pulmonary disease, and stroke and concluded subjects with comorbidities were frequently excluded from participating. Results show the situation is similar in MS clinical trials, where most exclude subjects with severe comorbidities or substance abuse. While exclusion of participants with comorbidities is intended to ensure participant safety, the consequence is a lack of knowledge about the safety, tolerability, and effectiveness of the studied treatments in people with MS who have common comorbidities.

[Data and safety monitoring](#) in clinical trials is a planned, ongoing process of reviewing study data with the primary purpose of protecting the safety of subjects, the credibility of the study, and the validity of its results. Typically, large studies, like those used to evaluate disease-modifying therapies (DMTs) for MS, establish a [Data Safety Monitoring Committee](#) (DSMC), which reviews trial conduct and accumulating data and makes recommendations regarding the ongoing safety of the trial subjects. When participants experience [adverse events](#) (AEs), the DSMC must decide whether these events are occurring at a greater than expected rate and whether or not they are treatment-related. In order to determine if an AE is occurring more frequently than expected, the DSMC must be able to determine the typical rate the illness or injury occurs in the population of subjects under study. According to the MSCP, a recent [review](#) identified very few studies evaluating the incidence of comorbidity in MS. Therefore, the information necessary to determine the significance of coexisting health conditions in MS clinical trials is not available. Frequently it is not until a new MS drug is released to the market that it is used in a



significant number (if any) of individuals with MS and other illnesses, and this is when data regarding AEs specific to people with MS and comorbidity can be collected. Unfortunately, post-approval safety is not monitored as systematically as it is in clinical trials.

As discussed in our [September 2017 newsletter](#), the [Belmont Report](#) established three basic ethical principals in clinical research: respect for persons, beneficence, and justice. **Respect for persons** dictates that individuals participating in research must be given the opportunity to choose what happens to them and those who are less capable are entitled to protection. This is the foundation for the informed consent process that is currently used in clinical research. The consent form must include sufficient information for potential subjects to understand the procedures, benefits and risks of a given study, and to make a voluntary choice to participate. **Beneficence** is the principal that clinical research should maximize possible benefits and minimize possible harms so that human subjects are not harmed. **Justice** requires the selection of research subjects be done in a manner that distributes the benefits and risks of research fairly. These three ethical principals are the cornerstones for regulations on research involving human subjects today.



The MSCP suggests considering whether to include or exclude subjects with comorbidity in clinical trials presents a potential conflict with these ethical principles. This is a frequent issue in MS clinical trials because comorbidities are common in people living with the disease. For example, older people (with MS and in general) typically have more concurrent illnesses. Many clinical trials have strict age

requirements that exclude these individuals. Increasing the age of enrolled participants and including those with comorbidities are ways to make MS study results more relevant to the general MS population. However, older individuals with MS may be less likely to benefit from the treatment under study (for a variety of reasons) and they may have an increased risk of AEs (both of which violate the principle of beneficence). On the other hand, excluding individuals with MS from clinical trials solely on the basis of age or comorbidity violates the principle of justice. Another issue is whether or not inclusion of participants with comorbidity may complicate interpretation of study data. Subjects with comorbid health conditions may not follow the assigned treatment as well, or may discontinue participation in a study prematurely. This would result in incomplete or inaccurate data. As discussed earlier, the converse would also be true. The validity of study results may be questionable if the subjects enrolled in the trial do not represent the “real world” population in which the treatment under study will be used (study results may not be applicable).

There is a desperate need for more clinical research into the impact of comorbidities in MS and their affect on MS treatments. According to [researchers](#) at Brigham and Women’s Hospital, people with MS are at an increased risk of [emotional disorders](#). These conditions are frequently undetected and inadequately treated in the MS population. Clinicians may have difficulty determining whether fatigue is due to MS or depressed mood and, therefore, selecting appropriate treatment. Individuals with MS may experience emotional symptoms while taking DMTs, corticosteroids, and other



medications. There is evidence that undetected and untreated mental illness may worsen functioning and quality of life, decrease treatment adherence and increase the risk of suicide in people with MS. After review of the current literature, investigators suggest more research is needed into these issues before recommendations on treatment can be made. For example, well-designed studies are needed on the [effect of interferon therapy on mood](#), as well as whether particular characteristics of individuals with MS might predict suicide. In addition, further study is needed on the effectiveness in people with MS of therapies frequently used in the non-MS population. A wide variety of medications and non-drug therapies are used to treat depressive and anxiety disorders in individuals with MS, but the evidence is insufficient to support or refute their use. This is a direct result of the frequent exclusion of people with MS from clinical trials. Investigators suggest improved detection, diagnosis, and treatment practices would significantly improve health outcomes in people with MS.

Concurrent health conditions are common in people with MS. Comorbidity affects the [safety and benefit](#) of many MS therapies, including those being tested in clinical trials. The eligibility criteria used in clinical studies often restrict subject enrollment based on comorbidities and factors that make secondary illness more likely (such as age). This creates a dilemma for MS researchers and people living with the disease. There is a tradeoff between focusing on a narrow subject population, which eliminates confounding factors and allows researchers to focus on select parameters in their studies, and the applicability of their findings in the real world. There is a tremendous need for more pragmatic study into comorbidities in MS and their affect on disease course and treatment.

