The challenge of comorbidity in clinical trials for multiple sclerosis

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For the attendees of the International Workshop on Comorbidity in Multiple Sclerosis

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ABSTRACT

Objective: We aimed to provide recommendations for addressing comorbidity in clinical trial design and conduct in multiple sclerosis (MS).

Methods: We held an international workshop, informed by a systematic review of the incidence and prevalence of comorbidity in MS and an international survey about research priorities for studying comorbidity including their relation to clinical trials in MS.

Results: We recommend establishing age- and sex-specific incidence estimates for comorbidities in the MS population, including those that commonly raise concern in clinical trials of immunomodulatory agents; shifting phase III clinical trials of new therapies from explanatory to more pragmatic trials; describing comorbidity status of the enrolled population in publications reporting clinical trials; evaluating treatment response, tolerability, and safety in clinical trials according to comorbidity status; and considering comorbidity status in the design of pharmacovigilance strategies.

Conclusion: Our recommendations will help address knowledge gaps regarding comorbidity that interfere with the ability to interpret safety in monitored trials and will enhance the generalizability of findings from clinical trials to "real world" settings where the MS population commonly has comorbid conditions. *Neurology*® 2016;86:1437–1445

GLOSSARY

MS = multiple sclerosis; **PRECIS** = Pragmatic–Explanatory Continuum Index Summary.

In 2005, more than 130 million Americans had one or more chronic health conditions.[1] Such findings are not restricted to North America.[2] Many individuals with a chronic disease will have another coexisting (comorbid) condition, and the likelihood of comorbidity increases with age. Comorbidity refers to the total burden of (chronic) illness other than the specific disease of interest.[3] Multimorbidity refers to the co-occurrence of 2 or more chronic conditions in an individual; it does not emphasize a specific index condition.[4]

Physical (medical) and psychiatric comorbidities are common in multiple sclerosis (MS).[5] Recent reviews suggest that the most common medical comorbidities in MS are hypertension, hyperlipidemia, and chronic lung disease while the most common psychiatric comorbidities are depression and anxiety.[5] Several studies suggest that comorbidity is associated with disability progression, lesion accrual on MRI, lower quality of life, hospitalizations, and mortality.[6–9]

However, little is known about how comorbidities influence MS-related treatment, including the decision to treat, the choice of agent, or treatment effectiveness, safety, tolerability, and

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adherence. Therefore, an international group of investigators in MS, epidemiology, clinical trials, and comorbidity met in Toronto, Canada, March 27 and 28, 2015, under the auspices of the International Advisory Committee on Clinical Trials in Multiple Sclerosis and sponsored by the European Committee for Treatment and Research in Multiple Sclerosis and the US National Multiple Sclerosis Society. This report describes the discussions and recommendations for addressing comorbidity in the context of clinical trial design and conduct in MS. We considered the effect of comorbidity on treatment in MS, eligibility for clinical trials, safety monitoring, and ethical issues.

EFFECT OF COMORBIDITY ON TREATMENT OF MS Literature regarding the effect of comorbidity on treatment of MS is limited. Findings in other chronic diseases suggest that comorbidity may affect multiple aspects of treatment. First, comorbidity may impede care. Individuals affected by multimorbidity report multiple barriers to self-care, including the compound effects of medications, difficulties in coordinating multiple medications, the total burden of medications, and financial challenges.[10] Second, comorbidity may affect the frequency or intensity of treatment of coexisting conditions.[11–14] Third, comorbidity may affect persistence or adherence (defined in Ref. 15) to treatment, further reducing the benefits of therapies, which are only partially effective. For example, depressed individuals with diabetes are 1.5-fold less likely to persist with pharmacotherapy for diabetes after 12 months of follow-up than nondepressed individuals.[16] Although the effect of comorbidity on persistence with MS disease-modifying therapies is unknown, depression is associated with reduced adherence to disease-modifying therapy (odds ratio 0.55; 0.42–0.74).[17] Findings on whether adherence improves after treatment of depression are inconsistent.[17,18] Fourth, comorbidity may affect the effectiveness, safety, and tolerability of treatment, although evidence for these issues is limited in MS. In a secondary analysis of longitudinal data from a randomized controlled trial of a teleconference-delivered fatigue management intervention for MS, comorbid diabetes or arthritis modified the response to the intervention. Individuals with diabetes improved more slowly after intervention than those without diabetes, while individuals with arthritis improved more rapidly than those without arthritis but they had difficulty sustaining improvements.[19] Finally, comorbidity may increase the risk of drug–drug and drug–disease interactions.

COMORBIDITY AND ELIGIBILITY FOR CLINICAL TRIALS Individuals with comorbidities frequently are underrepresented in clinical trials.[20] Therefore, trial findings may not apply to a typical clinic population with comorbidities. Boyd et al.[20] reviewed clinical trials identified using Cochrane reviews for diabetes, heart failure, chronic obstructive pulmonary disease, and stroke. These trials frequently excluded individuals with comorbidities, ranging from 0% to 44% of diabetes trials, 0% to 42% of heart failure trials, 0% to 55% of chronic obstructive pulmonary disease trials, and 0% to 39% of stroke trials. Moreover, only 43.5% (70/161) of the trials reported the prevalence of any comorbidity among participants. Information regarding the definition or ascertainment of comorbidity was limited. Only 3.1% (5/161) of trials used comorbidity as a subgroup variable. A review of randomized trials published in the 5 highest-impact general medical journals and specialized journals that focused on the most prevalent chronic conditions found that multimorbidity affected participant eligibility in 95% of trials.[21] Individuals with multimorbidity were excluded in 63% of the trials examined; this did not change from 1995 to 2010. Only 2.1% of trials explicitly included individuals with multimorbidity. A systematic review of 26 trials or prospective observational studies in cardiovascular disease focused on comorbidity measurement.[22] The comorbidities assessed varied across studies and were assessed using varied data sources with 35% not reporting the data source.

The situation is similar in MS where most pharmacologic trials exclude individuals with severe comorbidities or substance use disorders.[23–26] We reviewed the published results of 9 sentinel placebo-controlled trials of disease-modifying therapies approved for MS in the United States (table 1).[23–31] Five of 9 trials (55.6%) excluded individuals with various comorbidities. In 4 of those 5 trials, the description of the exclusions for comorbidities was vague,[25,29–31] making it unclear how they were operationalized. Uniformly, the way in which comorbidity was assessed for the purposes of eligibility was not reported. None of the trials described the comorbidity status of participants at enrollment. Furthermore, none considered the presence of comorbidity as a subgroup variable for a priori or post hoc analyses.

Although we did not review all clinical trials of nonpharmacologic interventions for managing symptoms of MS, an ongoing systematic review of comorbidity measurement in randomized trials of rehabilitation interventions suggests that comorbidities are only considered in relation to exclusion criteria and are rarely reported when participant characteristics are described (M. Finlayson, personal communication, 2015). For example, Oken et al.[32]

Table 1 Consideration of comorbidities in phase III placebo-controlled sentinel trials of disease-modifying therapies in MS

Author	Year	Trial name	Agent	Age range, y	Comorbidities excluded	Comorbidities reported as characteristics of study population	Comorbidities reported as adverse events
IFNB[23]	1993		Interferon-β-1b	18–50	None stated	None	Cardiac arrhythmia
Johnson[24]	1995		Glatiramer acetate	18–45	IDDM, positive HIV or HTLV-I serology, evidence of Lyme disease, required use of NSAIDs or aspirin during trial	None	
PRISMS[27]	1998	PRISMS	Interferon-β-1a	Not specified	None stated	None	Depression
Jacobs[25]	1996	MSCRG	Interferon-β-1a	18–55	Conditions other than MS compromising organ function	None	Depression
Hartung[26]	2002	MIMS	Mitoxantrone	18–55	None stated	None	Arrhythmia
Polman[28]	2006	AFFIRM	Natalizumab	18–50	None stated	None	Melanoma
Kappos[29]	2010	FREEDOMS	Fingolimod	18–55	Diabetes, immune suppression, clinically significant systemic disease	None	Neoplasms, macular edema, hypertension, AV block, hypercholesterolemia, depression
O'Connor[30]	2011	TEMSO	Teriflunomide	18–55	Other systemic diseases	None	Hypertension
Gold[31]	2012	DEFINE	Dimethyl fumarate	18–55	Another major disease that would preclude participation in a clinical trial	None	Neoplasms (renal failure)

Abbreviations: AV = atrioventricular; HTLV-I = human T-lymphotropic virus 1; IDDM = insulin dependent diabetes mellitus; MS = multiple sclerosis; NSAID = nonsteroidal anti-inflammatory drug.

randomized patients with MS to a weekly yoga class, weekly exercise class using a stationary bicycle, or a waiting-list control group. Participants with insulin-dependent diabetes; symptomatic lung disease; uncontrolled hypertension; liver or kidney failure; alcoholism/drug abuse; symptoms or signs of congestive heart failure, ischemic heart disease, or symptomatic valvular disease; or corrected visual acuity worse than 20/50 binocularly were excluded. A controlled trial of physiotherapy as intervention to improve mobility in MS excluded individuals with other major general medical or surgical disorders.[33]

While exclusion of participants with comorbidities is intended to ensure participant safety, the consequence is that we lack knowledge about the safety, tolerability, and efficacy of the studied regimens in persons with MS who have common comorbidities. Limited data suggest that safety and tolerability of disease-modifying therapies are affected by comorbidity. An observational study found that individuals with migraine have more difficulty tolerating interferon-β because of worsening headache profiles.[34] The risk of fingolimod-associated macular edema is higher among individuals with comorbid diabetes.[35] These issues are particularly important for future trials in progressive MS, in which the target population is likely to be older and, therefore, more likely to have comorbidity. Excluding individuals with comorbidities in these trials slows accrual and produces a study population that is even more divergent from clinical populations than trials conducted in relapsing-remitting MS.

EXPLANATORY VS PRAGMATIC TRIALS Randomized clinical trials can be classified as explanatory or pragmatic (table 2).[36] Explanatory trials test the efficacy of an intervention, that is, the effects under ideal conditions. An effort is made to enhance the internal validity of the trial by achieving a more homogeneous study population with well-specified inclusion and exclusion criteria, and by controlling all aspects of the intervention and comparator. In contrast, pragmatic trials test the effectiveness of an intervention, that is, the effects in real-world clinical settings where populations are more heterogeneous and differ from those in explanatory trials. Therefore, pragmatic trials produce findings that are potentially more generalizable and applicable to clinical practice. Clinical trials in MS to date largely have been explanatory in nature.

Although this classification suggests trials fall into distinct groups, explanatory and pragmatic trials really exist on a continuum, and several aspects or domains of a trial's design may influence where it falls in the continuum.[37] These may include eligibility criteria, the flexibility of the experimental and comparison interventions, required investigator expertise, choice of outcomes, intensity of follow-up and ascertainment of outcomes, and measures to ensure and assess adherence to the interventions by the participants and practitioners.[37] The Pragmatic–Explanatory Continuum Index Summary (PRECIS) tool and its subsequent revision (PRECIS-2)[38,39] were developed to assist trialists in considering these factors when designing their trials with the goal of matching

Table 2 Comparison of explanatory and pragmatic clinical trials

Explanatory	Pragmatic
Test efficacy: Does this intervention work under ideal conditions?	Test effectiveness: Does this intervention work under usual conditions?
High internal validity at possible expense of external validity	Improved external validity
Largely phase II–III	Largely phase IV
Smaller sample size	Larger sample size (to increase power to detect small effects)
Controlled environment	Full spectrum of routine clinical settings
Emphasize homogeneity of population and intervention, e.g.	Emphasize heterogeneity of population and intervention, e.g.
Restrictive inclusion/exclusion criteria	All participants enrolled regardless of expected risk, comorbidities, adherence
Instructions about applying intervention strict for all components	Instructions about applying intervention flexible
Select highly experienced practitioners	Include practitioners with range of skills
Outcomes focus on measurable symptoms or markers	Spectrum of outcomes, largely patient-centered
Shorter but intense follow-up	Longer, less intense follow-up
Adherence of participants and practitioners carefully assessed	Adherence is assessed minimally or not at all
Intention-to-treat analysis, possibly supplemented by per-protocol analysis	All patients

designs to the intended uses of the trial results. The tool could also be used to evaluate existing trials (for a more detailed description of PRECIS-2, see appendix e-1 on the *Neurology*® Web site at Neurology.org).

Pragmatic trials face challenges. Because the intervention(s) is not as tightly controlled, it may not be as well delivered, reducing its benefit. Increased heterogeneity and the dilution of the intervention's effect require larger sample sizes (discussed further in Ref. 40) and longer follow-up time, increasing costs and the risk of attrition. Although a pragmatic trial may be performed in multiple clinical settings, we cannot assume that the findings from one clinical setting translate to other clinical settings. Nonetheless, relaxing criteria regarding age and comorbidity status could enroll a population more similar to that seen in clinic settings.

COMORBIDITY AND SAFETY MONITORING IN CLINICAL TRIALS All clinical trials need safety monitoring. Typically, large randomized, multisite studies such as those used to evaluate disease-modifying therapies establish a Data Safety Monitoring Committee, which reviews trial conduct and accumulating data and advises the study sponsor regarding the ongoing safety of the trial participants. When participants experience treatment emergent adverse events including comorbidities such as hypertension, the Data Safety Monitoring Committee must decide whether the observed events are occurring at a rate greater than expected and whether they are treatment-related (i.e., a true safety signal) or not. Understanding how adverse events may affect differentially those with comorbidity is also important.

For common adverse events, the observed event rates can simply be compared between intervention groups, that is, using data internal to the trial. However, for rare (i.e., with a low event rate), serious adverse events such as cancers, the use of external comparators is needed. Such assessments require a good understanding of the expected age- and sex-specific incidence of comorbidities in the (untreated) MS population as these may differ from the rates reported for the general population. However, a recent systematic review identified very few studies evaluating the incidence of comorbidity in MS, with even fewer being population-based.[5] The most commonly studied conditions were cancer and epilepsy; however, the time period over which incidence was being studied was often unclear, the definition of the conditions varied across studies, and age- and sex-specific estimates were not generally reported. Thus, the information necessary to assess the significance of rare but clinically important adverse events is largely lacking.

Often it is not until a drug is released to the market that it is used in a significant number (if any) of individuals with comorbidities, and this is when adverse effects specific to individuals with comorbidity may be detected. However, postapproval, safety is not monitored as systematically at the individual or group level as in clinical trials. Although the strategies used for postmarketing surveillance vary somewhat across nations,[41] the challenges faced are similar. Postmarketing surveillance may involve one or more components including passive reporting of adverse drug reactions, active pharmacovigilance, phase IV studies, and the use of research networks to evaluate specific

adverse events of interest. Passive reporting systems underreport adverse drug reactions by as much as 98% as compared to systematic monitoring, and phase IV studies may not be completed as requested.[41] Specific efforts are required to assess the safety of new therapies in individuals with MS and comorbidities in the postmarketing phase.

ETHICAL ISSUES Consideration of whether to include or exclude participants with comorbidity in a clinical trial illustrates a potential conflict in ethical principles inherent in clinical trials. Because the lifetime prevalence of comorbidity in patients with MS is substantial, this issue is frequently encountered in MS trials. Expanding the age of enrolled participants and including those with comorbidities are ways to make the study population more typical. However, such individuals may have decreased likelihood of benefiting (i.e., violation of the ethical principle of beneficence) and an elevated risk of adverse effects (i.e., violation of the principle of nonmaleficence). There also may be concern that inclusion of participants with comorbidity may complicate interpretation of the trial if, for example, they adhere less well to assigned treatment or differentially discontinue treatment or trial participation prematurely.

These considerations are potentially in conflict with the principle of autonomy that states that unless the safety concerns are more than hypothetical, informed patients should have the opportunity to participate. Moreover, the external validity (generalizability) of the study is reduced if the trial population does not represent the clinical population in whom the therapy will be used. From an ethical perspective, the principle of justice suggests that particular individuals should not bear a disproportionate burden of research participation, nor should they be unfairly excluded from the potential benefits of participation. Thus, excluding individuals with MS from clinical trials solely on the basis of age or comorbidity status requires careful consideration of the reasons and ramifications.

RECOMMENDATIONS The workshop produced several recommendations to address knowledge gaps regarding the incidence of comorbidity that may interfere with the ability to assess safety in monitored trials, and the limited generalizability of clinical trials to clinical settings where the MS population commonly has comorbid conditions. These are described generally below and summarized in table 3 in more detail for the most common comorbidity, psychiatric comorbidity.

Establish age- and sex-specific incidence estimates for comorbidities in the MS population, including those that commonly raise concern in clinical trials of MS disease-modifying therapies. Comorbidities prioritized for future incidence studies were depression, anxiety, autoimmune disease, diabetes, cancer, hypertension, and migraine, based on several considerations. First, they may affect clinician-assessed, patient-reported, and imaging outcomes in MS, and health care utilization.[6–9,42] Second, they may affect adherence to treatment.[17] Third, they may affect the frequency or severity of adverse events.[35] Fourth, they may be

Table 3 Addressing psychiatric comorbidity in clinical trials for multiple sclerosis

Issues and strategies
1. Establish age- and sex-specific incidence estimates for depression and anxiety
2. For all clinical trial participants, report the severity of depression and anxiety symptoms using a validated tool and report histories of clinician-diagnosed depression and anxiety at baseline and at the end of the clinical trial
3. Obtain a preliminary assessment of the safety of the intervention of interest in persons with comorbid depression and anxiety
e.g., In phase II clinical trials, evaluate whether the intervention of interest worsens depression/anxiety symptoms using a validated tool (i.e., make this one of the relevant safety signals)
4. Based on phase II trials, consider inclusion of persons with depression and anxiety in phase III trials
e.g., If no safety concerns in phase II trials, allow inclusion of such individuals in phase III clinical trials unless the individual is suicidal or so mentally ill that participation is deemed to place the person at significant risk per the health care providers most responsible for managing their mental health
5. Ensure appropriate access to mental health care during the trial as needed
6. Monitor adherence of study participants to the intervention and evaluate whether this differs by psychiatric comorbidity status
7. Evaluate treatment response, tolerability, and safety according to psychiatric comorbidity status, as defined based on the lifetime history of psychiatric comorbidity and severity of depression and/or anxiety at enrollment
8. If sample size is thought to be a concern because of the inclusion of participants with depression or anxiety who may have heterogeneous responses or may be less likely to adhere to the intervention, investigators could set a threshold for the proportion of depressed/anxious persons who could be enrolled in the trial, as higher proportions of persons with comorbidities that may contribute to heterogeneity will increase required sample sizes[40]
9. Ensure that phase IV studies enroll persons with multiple sclerosis who are depressed or anxious and evaluate whether their risk of adverse events differs from that reported in phase III trials. The use of concomitant medications should be considered in these analyses

identified as adverse events in clinical trials; cancer and autoimmune disease were of particular interest in this regard.[43,44] Discussants also noted the importance of considering health behaviors such as smoking and obesity, as they are associated with the risk of developing comorbidities and may have independent effects on efficacy and safety.

Shift phase III clinical trials of new therapies in MS along the continuum from explanatory to more pragmatic trials. Specifically, we propose changes to eligibility criteria for clinical trials of pharmacologic and nonpharmacologic therapies. First, relax age restrictions. Second, consider relaxing restrictions on the inclusion of individuals with comorbidity. This has been feasible in other fields (table 4). Such decisions are a tradeoff between homogeneity of the population and the strength of the signal being sought, safety, and generalizability of the findings to clinical practice. We suggest that, in the absence of strong a priori safety concerns, individuals with the most common comorbidities in the MS population,[5] including depression, anxiety, hypertension, hyperlipidemia, and chronic lung disease, be considered for inclusion in trials. Furthermore, individuals with a history of cancer should also be considered as potential participants in some settings. These changes will be particularly important in trials in progressive MS, as these individuals will be older and will have a greater burden of comorbidity. These changes will require larger trials.

The comorbidity status of enrolled clinical trial populations should be clearly and consistently described. The description of clinical trial populations at baseline should include the prevalence of common comorbidities and whether they were currently treated (concomitant medications). These characteristics should also be updated and reported for the trial population as of the last study visit. Also, blood pressure, body mass index, waist–hip ratio, and current symptoms of depression and anxiety should be reported. To facilitate comparison of findings across clinical trials, we propose that, at a minimum, the presence or absence of the following diagnoses be reported: depression, anxiety, hypertension, hyperlipidemia, chronic lung disease (including asthma and chronic obstructive pulmonary disease), diabetes, autoimmune thyroid disease, migraine, and prior cancers. Ideally, these conditions would be verified by review of medical records and would not be based solely on self-report at the time of trial enrollment. For the measurement of current symptoms of depression and anxiety, it would be helpful if a single tool was used consistently in trials. Although several choices exist for depression, less work has validated scales for anxiety.[50,51] Further evaluation of the responsiveness of available tools in the MS population would assist in identifying the best instrument. A systematic review of the psychometric properties of depression scales is ongoing and may provide guidance.[52]

Evaluate treatment response, tolerability, and safety in clinical trials according to comorbidity status and health behavior status. Based on observational studies showing that comorbidity and health behaviors affect clinician-assessed, patient-reported, and imaging outcomes in MS,[7–10,42] it is likely that efficacy, safety, and tolerability differ by comorbidity status. This issue needs to be assessed to ensure that individuals with MS are not offered ineffective treatments while incurring risks. The initial focus of such subgroup analyses should focus on common, readily measured comorbidities such as hypertension, diabetes, smoking status, and obesity.

Comorbidity status should be considered in the design of postmarketing pharmacovigilance strategies. Phase IV studies should aim to enroll individuals with comorbidities and evaluate whether their risk of adverse events differs from that reported in phase III trials. The use of concomitant medications should be considered in these analyses. Research networks with access to large databases should be used to conduct studies to specifically assess the risk of significant

Table 4 Examples of pragmatic trials with relaxed eligibility criteria for age or comorbidity

Trial (name or lead author)	Question	Eligibility criteria regarding age and comorbidity	Trial registration
Price[45]	Are leukotriene antagonists equivalent to inhaled glucocorticoids as first-line management of asthma?	Age 12–80 y; excluded acute or chronic pulmonary processes; other comorbidities allowed	Controlled clinical trials no. ISRCTN99132811
WHICH? trial[46,47]	Is multidisciplinary management of patients with CHF post-acute hospitalization delivered in a patient's own home superior to care delivered via a specialist CHF outpatient clinic?	Age ≥18 y; excluded persons with a terminal condition likely to result in death or hospitalization within 12 mo	Australian New Zealand clinical trials registry no. 12607000069459
DRESS study[48,49]	Is TNF blocker dose reduction noninferior to usual care with regard to persistent disease flare in rheumatoid arthritis?	Only exclude persons with comorbidity if it also requires treatment with anti-TNF agents (e.g., Crohn disease) or when it is expected that the outcome cannot be measured (e.g., short life expectancy, planned major surgery)	Dutch trial register NTR3216

Abbreviations: CHF = chronic heart failure; TNF = tumor necrosis factor.

adverse events in individuals with comorbidities who use new therapies. The use of registries of all individuals using a novel therapy also may be helpful.

CONCLUSION Comorbidity is common in the MS population and affects safety and benefit of pharmacologic and nonpharmacologic therapies, including those being tested in clinical trials. The eligibility criteria used in trials that restrict participants based on comorbidities are a tradeoff between homogeneity of the population and the strength of the signal being sought, safety, and generalizability of the findings. The proposed recommendations are intended to allow clinical trials to better inform use of MS therapies in clinical practice.

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