Position paper
Towards a European Network for Multiple Sclerosis Trials (ENMST)

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Quality standards for clinical studies in the field of multiple sclerosis (MS) have improved significantly, to the great benefit of patients. This development has been accompanied by soaring costs and ever increasing complexity, with industry-independent trials having become virtually impossible. We propose establishing a European network that would include expertise in all the relevant aspects of MS treatment trials. In a stepwise approach, all interested active centres across Europe should be recruited into the network, based on agreement upon common scientific standards and quality requirements. Three main goals are discussed:

- to facilitate identification of potentially useful agents for MS treatment;
- to establish protocols for the interaction between investigators and industry; and
- to identify common standards and a core set of data to allow for comparisons of MS trials.

Collaboration with existing international organizations and institutions, especially the Sylvia Lawry Centre for MS Research, as well as with similar initiatives in North America and other parts of the world is envisaged.

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Introduction

Over the past decade, quality standards for clinical studies in health sciences in general, and in the field of multiple sclerosis (MS) in particular, have improved significantly, to the great benefit of patients. This process started due to increasing awareness of quality standards in the scientific medical community1 and was boosted over the past decade by stringent requirements of regulatory authorities for approval of novel therapeutic agents.2

This development towards better quality has been accompanied by soaring costs for clinical trials due to a large administrative overhead and ever increasing numbers of patients, as well as health care professionals participating in any given clinical trial. An average multicentre international Phase III trial in MS nowadays will cost in excess of €10 million. Industry-independent trials have thus become virtually impossible, since no public or other private organization is usually prepared to spend such a large sum on one individual project. This has resulted in a number of issues that need to be addressed. There are now few studies that are independent of industry and consequently there is a need to explore ways in which investigators collaborate with industry.3,4 A third issue, relating directly to inconsistent study design, is the lack of comparability of data between individual trials. These three issues identified in MS trials will now be discussed in more detail.

Lack of industry-independent studies

Trials have been and are set up to show statistical significance as early as possible for rapid submission to regulatory authorities. Often choices are more about extending the indications for an existing agent than exploring new and more relevant therapeutic strategies.5

Questions that are deemed to be ‘only’ of scientific interest, or that may risk shedding an unfavourable light on the product concerned, are usually insufficiently addressed.

Funding for long-term follow-up is sparse and often nonexistent despite the fact that these data are very relevant for clinical as well as socioeconomic reasons in determining whether an expensive MS treatment is only
Collaboration between pharmaceutical companies and clinical investigators

Raw data are usually considered proprietary information by the sponsor and only rarely made available for independent analysis. The final decision about when, how and whether data are publicly disclosed lies with the sponsor, often at the expense of publishing negative results.

The majority of clinical investigators have little or no influence on the trial design and analysis, particularly in large-scale trials, as they are usually invited to be involved late in the trial design. Their benefits are coauthorship, which in this situation does not reflect scientific input but mere participation, and monetary compensation. This may also lead to a conflict of interests for the author.\(^3,4\)

Most clinical investigators, even those invited to participate in trial design, do not have sufficient resources to allow them to be actively involved in management of the study, in data collection, verification and analysis. Therefore, even if companies grant access to primary data this is almost impossible to perform for practical reasons. (What investigator can afford to study hundreds of pages of computer output?)

These issues are particularly important in the light of the recent declaration by journal editors that they will not accept studies for review unless the investigators have unlimited access to the data.\(^5\) Many ethics committees are also making this a stipulation before a trial can begin.

Lack of comparability of data between trials

It is not unusual that several competing companies accumulate data on similar patient populations during clinical trials. Comparative analyses, which could be very helpful in patient management, have to date been impossible or performed by the companies themselves as investigators rarely have access to the respective databases. In addition, comparability is hampered by the lack of common standards for clinical trials in MS in terms of study population, duration of trial, timing of follow ups, clinical assessment and use of surrogate markers, particularly magnetic resonance imaging (MRI) measures. Sometimes, even basic definitions, such as who is to be considered relapsing–remitting or secondary progressive are not consistently used.\(^9\) In terms of outcome measures, there does not appear to be a consensus about what should be considered the most relevant parameter, and what should be used as a secondary measure to support the first.\(^10\)

The research community and patients alike would clearly benefit from improved comparability between trials that would allow more informed recommendations regarding treatment choices to be made. An important first step has been the creation of a large database at the Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR\(^11\)) which has incorporated the placebo groups of most clinical trials and several natural course cohorts. The next stage will involve the inclusion of data from treated groups in the database.

Strategy towards improvement

In order to improve the current situation, we propose establishing a ‘European Network for MS Trials’, which would include expertise in all the relevant aspects of treatment trials. This should include leading clinical MS research centres, with clinicians, radiologists, statisticians and laboratory scientists, who would be able to give advice and leadership for the planning and implementation of clinical trials in MS. We anticipate beginning with a small core of six to eight centres from several European countries that will agree on a program of common scientific standards and requirements for MS trials. In a second step, many if not all active centres across Europe will be recruited into the network. The three main aims of this network are the following:

- to facilitate identification of potentially useful agents for MS treatment;
- to establish protocols for the interaction between investigators and industry; and
- to set common scientific standards for all aspects of MS trials

To facilitate identification of potentially useful agents for MS treatment

Ideally, only substances of clinical importance with a realistic prospect of success should be tested in well-designed trials. Wasting resources carrying out studies of little scientific value should be discouraged.

To improve the scientific quality of industry-independent studies, the ENMST will help with organization of local or centralized funding for scientifically relevant (but not industry sponsored) trials or substudies in trials. It will help with organization of large-scale trials that are unlikely to be supported by industry, e.g., with older, cheaper drugs or with nonpharmaceutical interventions, like counselling or physiotherapy. It will also try to motivate and commit all investigators and centres of successful studies to long-term follow-up.

This will go hand-in-hand with the establishment of evidence-based treatment guidelines and determine the need for performance of the necessary trials in order to obtain more evidence for certain interventions. Ultimately, it will work towards the acceptance of these consensus rules by authorities and health insurance in individual countries.
To help increase quality and thus reduce waste of resources, the ENMST will establish, under the auspices of ECTRIMS, clinical and scientific standards for trial performance as well as ethical guidelines,\textsuperscript{12,13} e.g., on placebo-controlled trials.

By providing training possibilities and advice, it will help to assure that participating trial sites can meet the standards of clinical excellence and personnel requirements needed for a particular MS trial.

\textbf{To establish protocols for the interaction between investigators and industry}

These protocols should provide help for investigators and industry to address key issues in their collaboration in a timely manner. The following aspects will be covered:

- requirement of a sponsor independent, external advisory board and an investigator-driven steering committee early in the planning phase of the trial;
- definition of duties of the external advisory board and steering committee such as assurance of performance and financing of scientifically relevant additional or follow-up studies that may not be within the immediate scope of the sponsor;
- regulation of duties/responsibilities and rights of authors of publications of company-sponsored trials, including establishment of rules on accessibility of data to investigators and possibly external researchers (according to the rules set up by the editors of leading scientific journals) and empowerment of investigators to ensure optimum use of the data, e.g., by carrying out additional analyses to answer important scientific questions; and
- establishment of sample contracts between sponsors and investigators and advice in negotiations between individual trial sites and sponsors.

\textbf{To set common scientific standards for all aspects of MS trials}

Design and conduct of trials with MS patients, including the choice of outcome measure, length of follow up, method of data analysis, etc., should be further standardized in order to facilitate the comparison of data across different studies.

The ENMST will establish sample protocols for the various phases of development of new therapeutics in the different disease courses of MS, which will be adapted in line with latest developments. This would require a regular, comprehensive review of available clinical and laboratory data regarding methodological issues, such as sample size estimation, trial design considerations, stratification issues, patient selection criteria and surrogate markers.

Such sample protocols and advice for adapting them to a specific situation could be provided to interested companies. These activities should be conducted under the auspices of ECTRIMS, and in collaboration with other international organizations in the field of clinical MS research, including the European Charcot Foundation, European Platform, the Taskforce on Clinical Trials of the NMSS, USA, and the Consortium of MS Centres. Close collaboration with the Sylvia Lawry Centre for MS Research for independent and expert judgement on statistical issues, taking advantage of and contributing to its large database of clinical trial and natural course study data,\textsuperscript{11} is envisaged.

Funding of this Network in a first phase is sought by MS Societies, Charities and Public Research Funding Agencies. In a second phase, the Network would earn a significant part of its budget through collaboration with the pharmaceutical industry in planning and organizing trials.

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\textbf{References}