Frontiers of Neurology and Neuroscience

Vol. 39

Series Editor

J. Bogousslavsky  Montreux
The Right Therapy for Neurological Disorders

From Randomized Trials to Clinical Practice

Volume Editors

E. Beghi  Milan
G. Logroscino  Bari/Tricase

18 figures, 1 in color, and 16 tables, 2016
Contents

VII  Foreword
   Garattini, S. (Milan)

IX  Preface
   Beghi, E. (Milan); Logroscino, G. (Bari/Tricase)

1  The Basic Structure of a Randomized Clinical Trial
   Beghi, E. (Milan)

8  Peculiarities of Neurological Disorders and Study Designs
   Beghi, E.; Pupillo, E.; Giussani, G. (Milan)

24  Current Issues in Randomized Clinical Trials of Neurodegenerative Disorders at Enrolment and Reporting: Diagnosis, Recruitment, Representativeness of Patients, Ethnicity, and Quality of Reporting
   Logroscino, G.; Capozzo, R.; Tortelli, R. (Bari/Tricase); Marin, B. (Bari/Tricase/Limoges)

37  How to Distinguish between Statistically Significant Results and Clinically Relevant Results
   Bennett, D.A. (Oxford)

50  Modeling and Prediction in Neurological Disorders: The Biostatistical Perspective
   Copetti, M.; Fontana, A. (San Giovanni Rotondo); Pellegrini, F. (Cambridge, Mass.)

60  Composite Scores and Other Outcome Measures in Stroke Trials

71  Age, Comorbidity, Frailty in Observational and Analytic Studies of Neurological Diseases
   Novy, J. (Lausanne); Sander, J.W. (London/Chalfont St. Peter/Heemstede)

81  Disease Course, Outcome Measures, and Prognostic Predictors in Epilepsy: Opportunities for Improving Outcome of Drug Trials
   Schmidt, D. (Berlin)

93  Assessing Functional Decline in Neurological Diseases Clinical Trials: Duration of Follow-Up – The Case of Multiple Sclerosis
   Martinelli Boneschi, F.; Comi, G. (Milan)

101 Biomarkers in Randomized Clinical Trials: Magnetic Resonance Imaging
    Whitwell, J.L. (Rochester, Minn.)

109 Biomarkers in Randomized Clinical Trials: Positron Emission Tomography and Nuclear Medicine Techniques
    Singhal, T.; Stern, E. (Boston, Mass.)
117 Cerebrospinal Fluid Biomarkers for Target Engagement and Efficacy in Clinical Trials for Alzheimer’s and Parkinson’s Diseases
Parnetti, L.; Eusebi, P. (Perugia); Lleó, A. (Barcelona/Madrid)

124 Pharmacogenetics in Neurodegenerative Diseases: Implications for Clinical Trials
Tortelli, R. (Bari/Tricase); Seripa, D. (San Giovanni Rotondo);
Panza, F. (Bari/Tricase/San Giovanni Rotondo); Solfrizzi, V. (Bari); Logroscino, G. (Bari/Tricase)

136 Randomized Trials in Developing Countries: Different Priorities and Study Design?
Marin, B.; Agbota, G.C.; Preux, P.-M.; Boumédiene, F. (Limoges)

147 The Right Therapy for Neurological Disorders: From Randomized Trials to Clinical Practice – Patients versus Investigator Expectations and Needs
Bruijn, L.I. (Washington, D.C.); Kolb, S. (Norfolk, Va.)

154 General Overview, Conclusions, and Future Directions
Beghi, E. (Milan); Logroscino, G. (Bari/Tricase)

163 Author Index
164 Subject Index
The right therapy needs to be evidence based for neurological disorders just like all the diseases that afflict humankind. Evidence-based medicine requires randomized clinical trials (RCTs) to establish the efficacy and effectiveness of therapeutic interventions. RCTs, today mostly focused on drug evaluation, need to be extended to other treatments too, such as medical devices, electrical stimulation, surgery, nutrition, and rehabilitation practices. Moreover, many current therapeutic practices are still largely based on tradition and impressions, not on evidence. Even when a treatment is based on RCTs, frequently too few patients are enrolled and there may be biases that undermine the significance of the results.

This all reflects the vast economic interests that today surround medicine as a whole, and obviously also neurology. RCTs need to be conducted by independent organizations that may offer advantages over trials run by industry.

It may be worth very briefly mentioning the principal bias that is frequently detected. Selection of the population is certainly one of the main problems because it is very hard to balance the need for a homogeneous group of patients while at the same time covering patients likely to be encountered in current clinical practice. This usually results in an important imbalance concerning age and sex. Today almost 70% of drugs are used by patients older than 65; however, this population is underrepresented in most RCTs. These patients are no longer likely to have only a single disease, but because of their age they present polymorbidity and require polytherapy. These conditions are far removed from the clear situation of the RCT usually carried out in middle-aged males.

Females are also underrepresented in clinical trials and even when they are present it is difficult to find out from the trial publications whether they were even affected by the intervention similarly or differently from males.

The abuse of placebo is also very frequent in contrast with the ethical Declaration of Helsinki which requires comparisons with the best available treatment to avoid patients risking undue progression of their disease. Unfortunately, the approval of new drugs does not require comparative studies. In fact, the European directive specifies three requirements: quality, efficacy, and safety, but it does not require ‘added therapeutic value’. If it did, drugs would be better selected. A consequence of the fact that the European directive does not require superiority is that RCTs often set out to prove only ‘noninferiority’, which is ethically unacceptable because the null hypothesis is that the tested drug or treatment is worse than the treatment already available. Usually, it is promised that the noninferior efficacy is compensated by other advantages such as less toxicity. However, RCTs are mainly designed to establish benefits while adverse reactions can be detected only in clinical practice once the treatment has been available for several years.

Foreword
Clinical interventions must offer an outcome that is beneficial for patients, but RCTs often employ surrogate end points which are not always relevant to the patients’ quality of life. A typical case is a drug that reduces the volume of a tumor but does not affect what is important for the patient, i.e. overall survival.

Since RCTs will never be perfect, it is very important for the protocol to be registered in an easily accessible site and that the results always get published and raw data made available, under certain conditions, to independent investigators.

One of the main difficulties is making sure that results are not only dealt with in the scientific literature, but that they can be translated into clinical practice. It would therefore be useful if publications could include brief summaries of the clinical significance of the results. In particular, clinicians may appreciate knowing clearly how many patients need to be treated to ensure a therapeutic benefit in one patient.

This book, coordinated by Beghi and Logroscino, is a sort of compendium relating most of the principles of reliable RCTs to specific neurological diseases. The articles, written by specialized neurologists, have the merit of touching on important aspects of RCTs with a clear, critical approach. Neurologists involved in clinical trials will certainly learn a lot from this book, which should become a basic text for all neurological courses dealing with evidence-based neurology.

Silvio Garattini, Milan
The Treatment of the Neurological Disorders

Neurological disorders represent a relevant and ever-increasing fraction of the global burden of disease [1, 2]. As most neurological disorders are chronic and aging-related, with the increase of life expectancy and a decrease in age-specific mortality we expect a significant increase of their incidence and prevalence in the decades to come. The increase in frequency of neurodegenerative disorders will be a major part of another important phenomenon: the increase of life lived with disabilities. The trend will determine an increasing load on medical and social systems both in low- and high-income countries. There is thus a desperate need for successful preventive and therapeutic (curative) measures. During the last decades, a number of effective drugs have been made available to the benefit of patients with several neurological disorders, such as epilepsy, Parkinson’s disease, and multiple sclerosis. However, these drugs are symptomatic and at present there are no compounds apparently capable to abate or at least slow the progression of these diseases.

The lack of effective therapies has determined an increased role of prevention trials, especially in neurodegenerative disorders like Alzheimer’s disease. In the past decades, as with cardio- and cerebrovascular diseases, interventions modifying lifestyle (primarily physical activity and diet) have been explored for the prevention of cognitive decline in randomized clinical trials of individuals mostly in their midlife years. More recently, pharmacological prevention trials have also been started.

The picture is made even more complicated by the use of diagnostic tests with increasing levels of sophistication, which have brought the anticipation of diagnosis for some diseases to a subclinical (preclinical) level. In addition, genetic tests have added to the complexity of the spectrum of each disease with results not always understandable, given the frequent inconsistency of the genotype-phenotype correlations. Genetic tests have been rarely used in the stratification process in randomized clinical trials, with the sole exception of apolipoprotein E (APOE) in Alzheimer’s disease trials [3]. The spectrum of disease phenotypes has been largely expanded in the last few years due to new insights from genetics. A good example is the C9orf72 gene discovery that has linked frontotemporal dementia and amyotrophic lateral sclerosis [4].

In addition, epidemiological studies done in well-defined cohorts of patients with neurodegenerative disorders with prolonged follow-up have given further impulse to the characterization of the heterogeneity of chronic neurological disorders. All this is challenged by the external validity of the results of traditional clinical trials that are obtained from strictly homogeneous samples and, as such, are not applicable to all the aspects of the disease spectrum. The consequence is that the same treatment is offered to patients in whom
the disease has significantly different levels of severity (including cases that might never become symptomatic).

This is further complicated by the need to combine the clinical impact of the study results with the patients’ values and the interests of the pharmaceutical companies. Frequently, the needs expressed by the patients do not coincide with the expectations of the caring physicians, while big pharma prefers to invest in fields where the profit is not negligible. This reflects, on one side, the tendency to refrain from developing compounds to be used in rare diseases and, on the other side, to prefer the development of ‘me-too’ drugs or to magnify small, sometimes only subclinical, effects in the attempt to justify the earliest possible treatment.

Upon this background, a discussion has been started on the structure of the randomized trial to verify if and to what extent the present designs are suitable for proving the efficacy of an experimental treatment. Neurological conditions have peculiar features that may require the use of adaptive designs to address (and adjust for) the heterogeneous phenotypes and the differing levels of disease severity.

In view of the increasing number of biomarkers, disease-specific study end points must be defined, paying attention to the clinical relevance of each biological parameter. Then, in addition to the caring physicians’ therapeutic expectations, patients’ and caregivers’ needs must be more deeply considered when assessing treatment efficacy.

These aspects are the main objects of this book, the intent of which is to outline all the problems posed by acute and chronic neurological conditions and offer discussion points to the scientific community for the improvement of preventive and therapeutic strategies. International leaders in the field of neurological disorders have been invited to highlight this complex issue with the intent to provide a background for identifying the right therapy for neurological disorders in the near future. These experts have accomplished their task with examples from their specific fields of expertise. However, far from driving the reader’s attention away from the main focus of this book, these contributions help to shed light on the diverse and multifaceted aspects of major neurological diseases and provide scientists in charge of the design of therapeutic trials with all the elements needed to plan and conduct trials that can fulfill the unmet needs of scientists, caring physicians, and patients.

Ettore Beghi, Milan
Giancarlo Logroscino, Bari/Tricase

References