

DOI: 10.4103/ijmr.IJMR_70_17



The right therapy for neurological disorders: From randomized trials to clinical practice, E. Beghi, G. Logroscino, editors (Karger, Basel, Switzerland) 2016. 168 pages. Price: US\$ 155.00/CHF 132.00/EUR 123.00

ISBN 978-3-318-05864-2

The ultimate aim of any therapeutic strategy is the maximum restoration possible and eventual return to normalcy of function. There has been a steady increase in the number, complexity and evolution of 'new' diseases afflicting the nervous system, impacting the global disease burden in the society.

As most neurological disorders are chronic and ageing related, with the increase in life expectancy

and a decrease in age-specific mortality, we expect a significant increase of their incidence and prevalence in the decades to come. A major fall out of this phenomenon is an increase of life lived with disabilities. There is, therefore, an imperative need for successful preventative and therapeutic measures. The last few years have envisioned unparalleled advances in the understanding the pathology and pathophysiology of these diseases which has paved way for path-breaking advances in management strategies. In spite of these, there is a large proportion of untreatable and devastating degenerative diseases whose management and prevention remain nebulous at best. The picture is complicated by the availability of diagnostic tests with increasing levels of sophistication and cost. There is a further impact of combining the study results with the patient's interests and values.

This book essentially is a discussion on the design and structure of a randomized trial which can answer most optimally the relevant questions amongst the backdrop of these inherent vagaries and complexities of neurological disease which can potentially alter the relevance of interpretation of the study results.

The first chapter by describes a classical randomized controlled trial (RCT) which would represent the best model to assess the efficacy, tolerability and safety of any treatment for all clinical conditions including the neurological disorders. It reflects the need to disentangle the effects of the treatment from that of other prognostic variables. This may require a number of restrictions that are, at the same time, limitations for the application of the study results to the individuals who will receive the treatment in clinical practice.

The second chapter deals with the peculiarities and uniqueness of neurological disorders which need to be considered in designing clinical studies. Neurological disorders are inherently heterogeneous and this heterogeneity in clinical spectrum and course infuses bias if not carefully probed and addressed. Some of the diseases are represented by an acute monophasic course and have complete or partial regression to baseline. Others are characterized by recurrent episodes which also return to baseline or have a cumulative increase in deficits and disability. Others may have a relentlessly progressive and debilitating illness at various speeds. All these peculiarities and variations will have a strong influence on the effects of treatments and interventions. The RCT design therefore, must be adapted to the basic characteristics of each clinical condition. The chapter

goes on to discuss with individual references for diseases such as dementias, multiple sclerosis, stroke, and epilepsy emphasizing the same.

The variables and characteristics of a trial design which may alter the internal and external validity of an RCT are addressed in detail in the next chapter. This chapter emphasizes that the impact on phenotype at study entry has often been overlooked. Early diagnosis is challenged by phenotype, older age, female sex and comorbidities. Biological characteristics play a major role, but there is a need to estimate the importance of social factors affecting inclusion, such as access to specialized medical care, education and social status. There is a need for better consideration of key descriptive elements of the patients recruited, and the representativeness of the sample, in the results of the RCTs.

A quintessentially important aspect of any RCT lies on how to distinguish between significant and clinically relevant results. In order to be as effective as possible, health professionals need to be able to read and evaluate the findings produced by research in their chosen field. Critical appraisal of the evidence and being able to put that evidence into clinical practice is crucial for good clinical medicine. Various related approaches have been described in chapter 4, which should provide the practicing physician with a starting point to determine whether the reported significant results are indeed clinically relevant.

The biostatistical perspective of modelling and prediction in neurological disorders has been described in the next chapter. It describes how tree-based methods can represent a clinically interpretable and easy-to-implement approach for stratified medicine and treatment tailoring based on responsiveness as well as for selecting populations for new studies. The urgent need to improve the quality of designing, conducting analysis and reporting data from RCTs to obtain complete, clear and rigorous information on the effectiveness of management strategies in stroke care has been delineated in the subsequent chapter. The most challenging issue in comparing results from different stroke trials is coping with too many heterogeneous outcome measures. This heterogeneity is inherent in stroke outcome assessment due to the innumerable parameters which affect the disability. Use of composite measure derived from the combination of scores from multiple scales has been advocated in the past and probably will be the gold standard for future clinical trials.

Chapter 7 emphasizes the importance of age and comorbidities which should never be ignored in the observation and assessment of neurological conditions and their treatment. Most studies rarely take into account the comorbidities in the studies of neurological conditions and these prove to be a major confounder in assessing the outcomes of interventions. The opportunities for improving outcome of drug trials with special reference to epilepsy have been described in the following chapter. An in-depth analysis of the variabilities and uniqueness of disease course, outcome measures and prognostic predictors in epilepsy has been provided.

With reference to multiple sclerosis, the chapter 9 discusses how drug efficacy in reducing the short-term relapse rate and MRI activity impact on delaying the accumulation of long-term disability, in addition to summarizing the available literature from a few long-term extension RCTs on the long-term efficacy of available drugs.

Incorporating biomarkers of disease progression into RCTs which would be sensitive to the effects of disease-modifying treatments will be essential to validate the effectiveness of the interventions provided for the disease. An in-depth description of the biomarkers in RCTs with special reference to MRI has been provided in chapter 10. The next chapter deals with positron emission tomography and other nuclear medicine techniques as potential and viable

biomarkers for RCTs. Cerebrospinal fluid biomarkers for target engagement and efficacy in clinical trials for Alzheimer's dementia and Parkinson's disease have been delineated in chapter 12.

The role of pharmacogenetics in RCTs for neurodegenerative disease which is a potentially explosive and promising field of personalized medicine is still being explored to its full potential. Genetic testing allows increased sophistication in patient profiling and treatment optimization. Chapter 13 discusses this aspect in detail. The need for country-specific issues and prioritization for designing and conducting RCTs in the developing world has been described in the next chapter. The last chapter gives a synopsis of the entire collection of chapters in the book. Revision of the traditional structure of the RCTs to take into account the new perspectives of personalized and precision medicine is voted for.

The book ends well with a positive note. The indexing and references are also adequate. Overall, the book has concise, succinct information narrated with clarity and conviction.

M.V. Padma Srivastava
Department of Neurology,
All India Institute of Medical Sciences,
New Delhi 110 029, India
sakshisharma11189@gmail.com