Editorial

The N-MOmentum trial: building *momentum* to advance trial methodology in a rare disease

Jeremy Chataway

Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, UK

and

Tim Friede

Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

Corresponding author: Dr Jeremy Chataway

jeremychataway@googlemail.com

Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London WC1N 3BG, UK

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In Europe a rare disease is defined formally by a prevalence of less than 50/100,000.[1] So whilst adult MS is not rare, paediatric MS can be considered as such. How do you design a trial for a rare or orphan disease? A number of suggestions regarding innovative approaches to the design and analysis of trials in this arena have been made,[2] but current practice is often different and may shy away from implementing novel methodologies.[3] We therefore commend Bruce Cree and colleagues for developing and, even more importantly implementing, a new approach to a clinical trial in Neuromyelitis Optica (NMO) which is described in this issue of the MSJ.[4]

A cousin inflammatory condition of MS is of course NMO, which has only really split away from the main body of MS over the last decade, particularly with the discovery of the anti-AQP4 antibody. NMO is of major interest to those diagnosing MS because of the phenotypic similarities, sharpened by the differences in management. It is a rare disease, with prevalence rates of 0.5-4.5/100,000, with geographical variation (Japan versus Europe say). As is often the case in medicine, treatments have arisen through clinical judgement, to case reports, and then series, with the usual suspects being from the queue of: corticosteroids, immunoglobulins, plasma exchange, older immunosuppressants (eg azathioprine) and newer designer monoclonal antibodies (eg rituximab). But how to evaluate formally with randomised controlled trial (RCT) methodology a new arrival in a rare disease situation? What are the tricks of that trade? Matters are compounded by the potential seriousness of NMO: paraparesis and blindness stand out.

Here, the candidate to be evaluated is a new anti-CD19 antibody that depletes B cells and the trial is the N-MOmentum study [NCT02200770]. How do they do it and what statistical engine are they using? Their starting point, is that the evidence for current therapeutics is uneven (American Academy of Neurology class IV), made up of before and after studies, without control, and therefore a placebo arm is justified, but that the time spent on placebo should be minimised. The judgement of the appropriateness of a placebo arm in this condition is of course of great interest and could lead to a lively debate depending on practioner preference.[5] The ethical dimensions are well aired here.

In terms of pure trial design, four tactics were incorporated: a time-to-attack primary outcome; a short duration trial of 6.5 months; unbalanced (3:1) randomisation; and a futility analysis. How do these stack up statistically?

The use of the time-to-attack endpoint makes a placebo controlled trial feasible since treatments can be switched as soon as a relapse occurred, which is close to clinical practice and probably more comfortable. Exploitation of this makes placebo controlled trials possible in even more vulnerable situations such as paediatric diseases, for example the ongoing EARLY PRO-TECT Alport syndrome trial.[6] In an event driven trial such as the one suggested, statistical power is achieved by observing a certain total number of events, in this case 67 relapses. The short treatment of follow-up period of 6.5 months might appeal from an ethical perspective, but in fact has penalties for the sample size. The authors, using a meta-analysis of available data, estimate that a total number of 212 patients need to be randomized to achieve the target number of relapses. If the follow-up period was say 12 months rather than 6.5 months, the sample size could be reduced by more than 40%, with clear advantages in terms of rates of recruitment and number of centres. It is indeed a

difficult tightrope to walk to satisfy all the relevant parties. Unbalanced randomization is a good move, since it makes participation in the trial more attractive to the patients and provides additional and very valuable on-treatment data (such as safety) at a fairly small cost in terms of increase in sample size. Futility analysis is a design feature more often seen recently because of its obvious appeal from an ethical standpoint but also as a means to protect time and resources.[7] Furthermore, the interim analysis provides an opportunity to adjust the preplanned sample size if the relapse rates turns out to be lower than expected.[8]

Finally, in rare conditions we should be more open to incorporating data external to the randomized controlled trial. This includes (control) data from previous trials, natural cohort studies, and clinical registries. This is termed generalized or cross-design evidence synthesis. Technically these are extensions of the standard random effects meta-analysis methodology, which itself presents some caveats in rare disease settings.[9] However, promising examples are starting to appear in the literature.[10] How and when these techniques will also be applicable in confirmatory settings, will need more discussions with stakeholders including regulatory agencies, and most importantly, convincing examples of success.

Ultimately, of course the aim is to find effective treatments for devastating conditions as quickly as possible. The N-MOmentum trial, confronts the issues, ethical and statistical head on, and the final results and knowledge gained will be eagerly awaited to provide *momentum* to advance trial methodology in rare diseases, both in neurology and elsewhere.

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Conflicts of interest

JC declares none relevant to this article

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