Adaptive clinical trials incorporating treatment selection and evaluation: Methodology and application in progressive multiple sclerosis

Richard Nicholas[1], Jeremy Chataway[1,2], Susan Todd[3], Nigel Stallard[4], Elsa Valdés-Márquez [3], Nicholas Parsons[4], Tim Friede[4]

[1]Imperial College Healthcare NHS Trust, London
[2]National Hospital for Neurology and Neurosurgery, London
[3]Applied Statistics, The University of Reading
[4]Warwick Medical School, University of Warwick

Introduction
In progressive multiple sclerosis (MS) irreversible disability often takes many years to accumulate as a result prolonged trials are required to assess the benefits of therapies. There is a need to understand the relationship between short-term outcome measures such as MRI endpoints and long-term clinical outcomes in progression to determine the evolution of the disease early on. Thus, the common phase I-II-III paradigm for clinical trial design with separate trials for each phase may not be appropriate.

Methods
We implemented a seamless adaptive design for progressive MS. Extensive statistical simulation studies based on real data were used to evaluate different trial designs including treatment selection rules, sample sizes and time point of interim analysis in terms of power and treatment selection probabilities. For these simulations to be as close to clinical practice as possible a comprehensive literature search was carried out identifying 1087 abstracts and six clinical databases were analyzed.

Results
We derived a feasible adaptive trial design for application in progressive MS. Simulation studies, performed using MRI lesion load/T2 lesions for the interim outcome and extended disability status scale (EDSS) as the final clinical outcome, found that practical powerful designs could be derived, allowing treatments to be selected during the trial without compromising control of the false discovery rate (type I error rate).
Though correlations between early outcomes (e.g. MRI after one year) and disability outcomes (e.g. EDSS) at end of study are generally low (in the range of 0.1 to 0.25), adaptive treatment selection is still a viable option as long as the ordering of treatments by effect size is not vastly different on the early outcome scale compared to the disability outcomes.
A gain in power (or savings in sample sizes) compared to traditional designs could be demonstrated and recommendations for design options such as the time point of the interim analysis could be derived from the simulation results.

Conclusions
Adaptive designs are applicable to progressive MS and practical with current available interim and final outcome measures. They require significantly fewer control subjects and allow testing of multiple therapies simultaneously and eliminate wasted time between phase II and III. Newer interim outcomes such as MRI atrophy data may further increase the power by increasing the correlation between the interim and final outcomes.