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

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Background

Despite the advent of a raft of novel drug strategies in MS which reduce relapse rate, the problem of trying to slow or stop disease progression remains. This applies both to primary (PPMS) and secondary progressive (SPMS) disease states, the latter typically occurring 10-15 years after disease onset. In this context, novel strategies for trial design are required that allow a number of putative compounds to be tested, dropping after a first stage drugs which appear to have no significant effect on disease progression, whilst taking the promising compounds to the next stage.

Adaptive Trial Design

The focus of this work is the development of methods for comparison of a number of experimental treatments with a common control in a single study with two distinct stages. Patients will be recruited over 2 years and followed up for 3 years (Fig. 1). At the end of the first stage, after between 1 and 2 years, an interim analysis of data on an 'early' outcome measure will be used to select treatments for stage 2. At the end of stage 2, inference will be based on the 'final' outcome measure for all patients recruited from both stages.

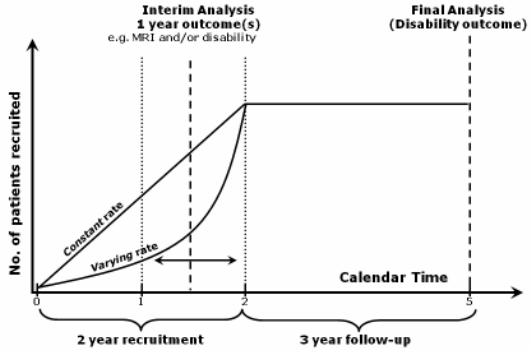

Figure 1. Recruitment and follow-up of patients

An example trial design for 4 test treatments and a control (placebo) group is shown in Figure 2.

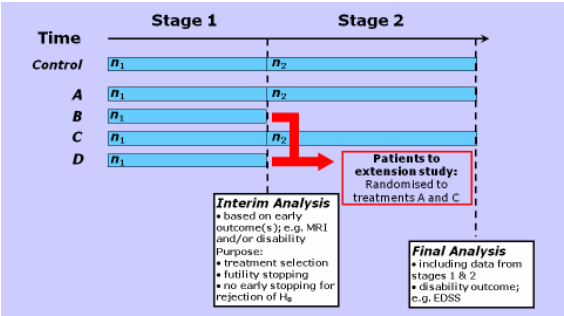

Figure 2. Design for 4 treatments and a control, with n_1 patients in each group at stage 1 and n_2 patients in each group at stage 2

Literature Review

A comprehensive review of the available literature was undertaken to inform the simulations. This identified 1087 abstracts, and also 9 clinical databases (including about 1500 patients) were obtained, from UK MS centres/SLC, and analyzed.

Simulation

A simulation study was conducted to investigate a range of potential options for the trial design including when to carry out the interim analysis and how to select treatments at the interim analysis. These are virtual trials based on realistic assumptions about the distributions of the endpoints, effect sizes, correlations etc, using information from available data, literature review and expert opinion. A set of modular functions (Fig. 3) were developed in the R (www.r-project.org) statistical programming environment to implement the simulations.

Results

The curves (Fig. 4) show the power to successfully detect a single effective treatment from 4 test treatments plotted against the total trial sample size (patients) for a flexible selection rule and a conventional (phase II and phase III) design. Many thousands of plausible clinical scenarios were tested, using a range of design options and assumptions.

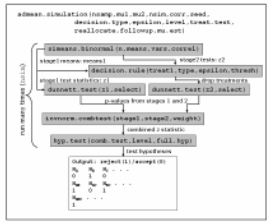

Figure 3. Structure of R functions for implementation of ASD

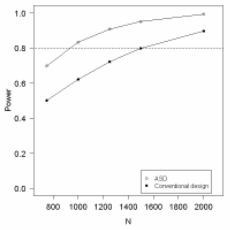

Figure 4. Power curves comparing ASD to a conventional design

Conclusions

- This is the first time that adaptive seamless designs (ASD) have been suggested, developed and shown to be feasible for secondary progressive MS.
- The ASD approach combines the 'conventional' phase II and III stages of a clinical programme into a single study and thus provides savings by requiring fewer patients.
- ASD based on early outcomes performs well provided we have a 'biologically plausible' outcome measure for treatment selection. This concept differs from a 'surrogate' marker, in that it only has to give some indication as to whether the treatment is working or not, rather than making predictions for treatment effects on the long term clinical outcome.
- When information is available on two key design options, the number of test treatments and the likely treatment effect types, a definitive statement giving optimal settings for the design parameters of a future study can be made.

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MS-AD web pages: http://www.warwick.ac.uk/go/ms_adaptive