

Alternative designs for phase II MS-trials

Diploma thesis – Abstract

The topic of this thesis was initiated by the Sylvia Lawry Centre for Multiple Sclerosis Research (SLC). The SLC is an international centre, which was established to support research into the causes of multiple sclerosis (MS) and to accelerate the development of effective therapies.

From a multiplicity of thereby arising questions two topics were selected which this thesis deals with.

The **first part of the thesis** consists of an analysis of homogeneity. The question that should be addressed is, whether the pooling of different trials of the SLC database to one dataset and thereon based analyses are acceptable. Classical linear modeling and an analysis of variance, as well as a Bayesian approach have been used. To clarify whether different trial specific technical settings of the MRI change the endpoints considerably, and whether the heterogeneity in the trials can be attributed to this.

The analysis is based on placebo data of phase II and phase III trials.

The result is that analyses based on the pooled database need an adjustment for the trials.

It can not always be assumed that different settings of the technical parameters can explain the existing trial effects.

The **second part of the thesis** deals with alternative designs for phase II trials.

Thereby the group sequential design of Pocock (1977) and the adaptive design of Bauer and Köhne (1994) were considered.

A simulation study for the two designs with one interim analysis was performed with the possibility to adapt the trial protocol after the first stage of the trial. Mean and median numbers of patients necessary for various settings of power and treatment efficacy have been simulated based on the pooled SLC dataset. The main result of these simulations is that alternative designs are suitable for this kind of MS clinical trials. By the possibility of an early stopping of the trial and a resulting reduction of the number of patients costs and time can be saved. On the basis of these alternative designs a re-analysis of four clinical trials was performed. Thereby it should be examined whether the trials could have been stopped early with the appliance of these designs. This would have led to an earlier application of effective therapies or to a reduction of risk by stopping for futility.

The result of this re-analysis is that the used datasets are not well suitable to show the advantages of the alternative designs.

Only in a few constellations the trials could have been stopped early and therefore the number of patients could have been reduced. This is partly due to the fact that hardly any therapy effect was detected in the four studies used for the re-analysis.