

Group sequential designs for three-arm 'gold standard' non-inferiority trials

In the recent years there have been numerous publications on the design and analysis of three-arm 'gold standard' non-inferiority trials. Whenever feasible, regulatory authorities recommend the use of such trials in order to obtain reliable study results and to maintain assay sensitivity. Nevertheless, it is desirable in many respects, e.g. ethical reasons, to keep the placebo group size as small as possible.

We present two approaches for group sequential designs that reduce, on average, the sample sizes in a three-arm non-inferiority trial. Both approaches consider the following two hierarchically ordered hypotheses: (I) superiority of the experimental treatment to placebo, (II) non-inferiority of the experimental treatment to the active control. In the full group sequential design both hypotheses (I) and (II) are tested in a group sequential manner, whereas in the partial group sequential design only hypothesis (I) is tested group sequentially and hypothesis (II) is analysed with a common fixed size sample test. The first approach aims on a reduction of the overall average sample size, whereas the second one reduces only the expected placebo group size while keeping the maximum sample sizes close to the single stage sample sizes.

We illustrate both approaches via numerical calculations and a comparison to the fixed design. Furthermore, we will address the impact of the group sequential boundaries on key characteristics such as the maximum and average sample sizes.