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## **Planning and Analysis of Two- and Three-Arm Non-Inferiority Trials**

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Two-arm non-inferiority studies comparing an experimental treatment to a reference therapy have meanwhile become an important tool to establish the efficacy of a new treatment. A new treatment which is at most by a clinically irrelevant amount inferior to the reference concerning efficacy may be preferred by patients due to advantages in another field, as for example, better tolerability, less potential for interactions, easier administration etc. Although there are numerous difficulties related to two-arm non-inferiority trials which can lead to less credible results than those of placebo-controlled trials, a new treatment should always be tested against the best current available method. Moreover, it is not always feasible for ethical reasons to incorporate a placebo control in addition to the two treatment arms considered and to perform a three-arm trial. Consequently, there will always be a need for both two- and three-arm non-inferiority trials. For diseases where it is ethical to include placebo in the trial, a three-arm non-inferiority trial is the preferred design and represents the scientific gold-standard.

The work essentially focuses on the planning and the analysis of two- and three-arm non-inferiority trials. The planning of these clinical trials covers the calculation of the sample sizes required to detect a minimally clinically relevant difference with a given power as well as the determination of an optimal allocation of the patients to the two or three groups, respectively, minimizing the total sample size. The scenarios of continuous, binary, and Poisson distributed outcomes were considered as special cases.

For two-arm non-inferiority trials with continuous or binary outcomes, existing sample size formulae were presented and optimal allocation ratios were determined. In case of Poisson distributed count data, no closed form expression for the sample size calculation is available and given in literature up to now. We derived asymptotic tests and related approximate sample size formulae for Poisson outcomes that may be observed within unequal follow-up schemes. The proposed test showed favorable type I error control and can be recommended for practical application. Moreover, the corresponding approximate sample size formula turned out to be very accurate even for small sample sizes.

For three-arm non-inferiority trials, we provided a method to calculate the required sample size that takes into account the correlation structure of the test statistics. This proposed approach leads to considerable savings in sample sizes as compared with application of ad hoc methods for all three scale levels. Furthermore, optimal sample size allocation ratios were determined that result in markedly smaller total samples sizes as compared with equal assignment. As optimal allocation makes the active treatment groups larger than the placebo group, implementation of the proposed approach is also desirable from an ethical viewpoint.

Besides the planning of two- and three-arm non-inferiority trials, we investigated the analysis of these designs. We adapted a flexible testing strategy, originally proposed for subgroup analysis, to multiple testing problems in non-inferiority trials. This flexible method allows the testing of a secondary hypothesis in a confirmatory way, even if significant results in the primary comparison could not be shown. The flexible multiple testing strategy was compared to the conventionally applied stepwise procedure. The proposed testing strategy leads to a more flexible testing of multiple hypotheses and works as a kind of 'rescue method'.

Clinical trial examples were used to illustrate all derived methods. Moreover, all programs that can be used for sample size calculation in two- and three-arm non-inferiority trials are provided.

In summary, this work provides methods for sample size calculation in two- and three-arm non-inferiority trials that lead to a marked decrease in the required sample size as compared with conventional approaches. Moreover, the application of the multiple testing strategy in the context of two- and three-arm non-inferiority trials results in a more flexible testing of the hypotheses. Hence, this thesis gives innovative and efficient procedures for planning and analyzing future non-inferiority trials.