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Network Meta-Analysis with a Focus on Cluster Randomized Trials

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This thesis focuses on the research field of network meta-analysis which experienced a lot of interest in the last few years. In a broader sense, meta-analysis is the methodology to pool results from clinical trials. In a classical pair-wise meta-analysis, only two-arm trials can be combined. Network meta-analysis is an extension to a multi-arm data setting.

In the first chapter of this thesis, a short introduction to the research field is presented. The importance of meta-analysis, in general, and of network meta-analysis as a further development is pointed out.

In the second chapter, an overview of pair-wise as well as network meta-analysis is given. The models, the estimation procedure as well as the interpretation of the results are presented and discussed. In addition, the challenges that arise, when results from clinical trials are pooled, are addressed. This includes heterogeneity, which describes the divergence amongst the estimated effects from different trials comparing the same treatment arms, as well as inconsistency, which denotes the discrepancy between direct and indirect comparisons of treatment arms. Furthermore, the characteristics of Bayesian and frequentist approaches as well as their similarities and differences are presented.

In the third chapter, the inclusion of cluster randomized trials in a network meta-analysis is considered. First, Bayesian approaches to include clustered data in pairwise meta-analysis are presented and, after this, the ideas are extended to a multi-arm setting. Different approaches are compared. The main problem is that the variance structure has to be taken into account properly when the treatment effects are examined. There are different ways to realize this. We can either adjust the data itself or the models that are used in the estimation procedure. The different approaches are presented and discussed. After this, the approaches are compared in a simulation study. A data example that is based on a real data set is used for illustration. In conclusion, it became clear that not all approaches are suitable for use in practice, since some of them lead to biased results or do not control the type I error rate. However, there are adjustments to the original approach that accurately take account of the clustering structure in the data. A discussion of the findings and a conclusion with practical advice and concrete suggestions is presented in the final section. Furthermore, an outlook to methods for individual patient data is provided with a small simulation study for an orientating evaluation of the characteristics.

In the fourth chapter, an estimation of the probability that a treatment arm leads to a more favorable result than another treatment arm is presented. This probability is very useful to compare the efficacy of treatments. In addition, it is shown how this probability can be used for hypothesis testing of treatment effects in a network meta-analysis. The main application is to test for differences between a new and a standard treatment. The approach can be extended to a non-inferiority setting as well as to a test for relevant superiority. It can be implemented in a straightforward way and is, thus, very useful in practice. The approach was evaluated in simulation studies. A real data example was used for illustration. In conclusion, the test procedure has very good properties and leads to valid results as it maintains the type I error rate. Thus, it can be recommended for use in practice to test for treatment differences in a network meta-analysis.