Summary

Chapter 1, the general introduction, gives an overview of the background and aims addressed in this thesis. Randomized clinical trials (RCTs) provide the most reliable evidence of effectiveness of medical interventions. Specific challenges with regard to efficiency arise when conducting RCTs in rare diseases in heterogeneous populations are challenging. Despite the random allocation between treatment- and control group, differences in baseline risk on outcome can arise between the treatment arms, simply due to chance. Also, in diseases with large heterogeneity in natural disease course, severity and outcome, small differences in baseline risk on outcome between the treatment arms may have influence on the treatment effect estimated.

When performing an RCT is impossible, the quasi-experimental "regression discontinuity" (RD) design is an alternative epidemiological design to study effectiveness of a medical intervention. In the RD design, treatment is not assigned randomly like in an RCT, but is allocated to a subset of patients, based on a cut-off of a baseline assignment variable. A subset of patients below the cut-off, not receiving a medical intervention, is considered as the control group. Due to the controlled treatment assignment, an RD design achieves balance on unobserved factors between the treatment- and control group, just like in an RCT. RD may thus provide an opportunity to obtain unbiased causal treatment effect estimates, when an RCT is not feasible.

The aim of this thesis was to assess the benefits of more advanced statistical analyses to estimate treatment effects from RTCs in heterogeneous diseases (part I; chapter 2, 3 and 4). Besides, the validity and reliability of the RD design compared to an RCT to estimate causal treatment effects was studied (part II; chapter 5, 6 and 7).

In **chapter 2** we found that hospital admissions for Guillain Barré syndrome (GBS) patients were heterogeneous, especially with regard to number of transfers and costs. GBS is a complex disorder because of the various stages in the clinical course and diversity in clinical course between patients. The complexity is reflected in the high frequency of transfers between departments and hospitals, especially shortly after initial admission. Transfers within and between hospitals were frequent: 40% of the patients were transferred at least one time and half of them were transferred within two days of admission. Moreover, in 25% the admission may have been suboptimal form a cost-effectiveness perspective, including admission to other than (pediatric) neurology departments or ICUs, admission of mildly affected patients to ICUs and transfers shortly after the initial admission. The related costs were highly variable between patients and mainly associated with the severity of disease. The large heterogeneity should be taken into account when designing an RCT in GBS.

In **chapter 3**, we studied the prognostic value of major extracranial injury (MEI) on mortality in traumatic brain injury (TBI) patients. Our results show that MEI is an important prognostic factor for mortality in TBI patients. However, the prognostic effect is dependent on the population studied. First the strength of the effect is heterogeneous

over the range of the brain injury severity. The prognostic effect of MEI is larger in patients with mild TBI. Moreover, we found that the effect is dependent on the time of inclusion in a study. In the registry we used in our study, MEI is strongly associated with mortality after adjustment for age, Glasgow Coma Scale motor score and pupil reactivity. In broadly selected observational studies and an RCT, including TBI patients surviving the early stage after their injury, the incremental prognostic value of MEI compared to known predictors of mortality was limited. These results are important for example to identify prognostic variables for covariate adjustment, in the design of future TBI trials. Our meta-analysis implicates specifically that MEI is an important prognostic factor to correct for when studying the effect of pre-hospital interventions, including all patients starting from the time of injury. In contrast it would be less urgent to consider MEI in studies assessing in-hospital interventions, including mainly patients with more severe brain injury and patients who survived the early phase after injury.

In **chapter 4** the benefits of both covariate adjustment and proportional odds analysis in RCTs in GBS were assessed. On expectation, covariate adjustment leads to more extreme (further away from $\beta = 0$ *or odds ratio* = 1) treatment effect estimates and larger standard errors. Indeed, we found increased standard errors in all adjusted analyses compared to the unadjusted analyses. The better prognosis in the treatment group decreased the treatment effect estimate β after covariate adjustment in the Plasma Exchange vs Intravenous Immunoglobulin (PE vs IVIg) trial. In the IVIg and placebo versus IVIg and Methyl-Prednisolone (MP) (IVIg vs MP) trial, the treatment group had a lower probability of favorable outcome. Therefore, in the IVIg vs MP trial covariate adjustment led to a larger β and a smaller p value. The potential gain of proportional odds analysis was also assessed. The proportional odds analysis estimates the treatment effect on each cut-off of the ordinal outcome scale, instead of estimating the treatment effect on the difference between the averages scores in the treatment arms, as in linear regression. Because the ordinal analysis uses the full ordinal outcome scale instead of one dichotomy, the variability will be smaller compared to binary analysis. This was confirmed in our study, where the proportional odds resulted in lower standard errors compared to the binary approaches.

Chapter 5 describes simulations and a validation study to assess the validity and efficiency of the RD design with continuous outcomes, compared to an RCT. In both the simulations and the validation study the treatment effect estimates from an RCT were used as the reference for a prospectively performed RD. We estimated the treatment effect using linear regression adjusting for the assignment variable both as linear terms and restricted cubic spline (RCS) and using local linear regression models. In the first validation study, the estimated treatment effect β from a cardiovascular RCT was −4.0 mmHg blood pressure (95% confidence interval (CI): −5.4, −2.6) at 2 years after inclusion. the estimated effect in RD was −5.9 mmHg (95% CI: −10.8, −1.0) with RCS adjustment.

RD showed different, local effects when analyzed with local linear regression. In the second RCT, RD treatment effect estimates on total cholesterol level at 3 months after inclusion were similar to RCT estimates, but at least six times less precise. We concluded that RD may provide similar estimates of treatment effects to RCT estimates but requires the assumption of a global treatment effect over the range of the assignment variable. In addition to a risk of bias due to wrong assumptions, researchers need to weigh better recruitment against the substantial loss in precision when considering a study with RD versus RCT design.

In **Chapter 6**, we aimed to evaluate validity and efficiency in the RD design for dichotomous outcomes compared to an RCT. We hereto performed validation studies in three large RCTs. To mimic the RD design, we selected patients above and below a cutoff (e.g., age 75 years) randomized to treatment and control, respectively. Adjusted logistic regression models using RCS and polynomials and local logistic regression models estimated the odds ratios (ORs) for treatment, with 95% CIs to indicate precision. In the first RCT, treatment increased mortality with OR 1.22 [95% CI 1.06e1.40] in the RCT. The RD estimates were 1.42 (0.94 - 2.16) and 1.13 (0.90 - 1.40) with RCS adjustment and local regression, respectively. In the second RCT, treatment reduced mortality (OR 0.83 [0.72 - 0.95]), with more extreme estimates in the RD analysis (OR 0.57 [0.35 - 0.92] and 0.67 [0.51 - 0.86]). In the third RCT, similar RCT and RD estimates were found, again with less precision in RD designs. We concluded that the RD design provides similar but substantially less precise treatment effect estimates compared with an RCT.

Although we know that the RD design may provide valid treatment effect estimates, the design is inefficient. In **chapter 7** we aimed to compare different assignment approaches to increase the statistical efficiency in RD. In Monte Carlo simulations, a random (R^2=0), low (R^2=7%) and highly (R^2=31%) correlating variable with outcome was used for treatment assignment. Patients were sampled from the CRASH trial, with a dichotomous outcome simulated. The treatment effect was analyzed with both local logistic regression and logistic regression with spline adjustment. To assess the relative statistical efficiency, standard errors (SE) of the different treatment assignment strategies were compared with an RCT of the same total sample size. This procedure was repeated in CRASH (n=9,554) as a case study. In the simulations, treatment effect estimates were unbiased. To obtain the same efficiency as an unadjusted RCT, RD required 2.8 times as many patients when using an assignment variable not correlating with outcome, and approximately 3.3 times as many patients when using an assignment variable highly correlating with outcome, using local regression. Compared to an adjusted RCT, the relative efficiency was not dependent on the correlation between the assignment variable and outcome since the adjustment affects the efficiency of an RCT as well. In the case study similar results were found.

Chapter 8, focusses on implications and recommendations when designing an RCT or RD to study the effectiveness of a medical intervention. When designing a future RCT in heterogeneous diseases we recommend de following:

- Covariate adjustment and proportional odds analysis most efficiently use the available trial data and ensure balance between the treatment and control group to obtain reliable and valid treatment effect estimates. These methods merit application in future trials in rare and heterogeneous neurological diseases like GBS.
- To apply covariate adjustment in future trials good knowledge of the prognostic value of baseline characteristics is crucial to pre-specify the variables for covariate adjustment. These variables can be identified based on clinical experience and past literature on the prognostic value of baseline characteristics.
- The common OR from a proportional odds analysis is a fair representation of the effect of treatment on the (ordinal) outcome. Moreover, this approach is more efficient compared to the binary approach. Therefore, we recommend the use of the full ordinal outcome scale in future trials in rare and heterogeneous neurological diseases.

However, when an RCT is impossible, an RD design can be considered and is preferred over an observational design to assess effectiveness of a medical intervention. Summary implications and recommendations to use RD in epidemiologic and clinical research can be made:

- In an RD design we have full understanding of the allocation of treatment, in contrast to observational studies. The treated- and control patients are replaceable around the cut-off of the assignment variable. This enables local causal inference.
- The RD design may result in similar treatment effect estimates compared to an RCT but are substantially less efficient than the RCT estimates. A prospective RD design needs much higher patient inclusion than RCTs. Otherwise, large observational registry data should be available to apply a retrospective RD.
- RD estimates should primarily be interpreted as local treatment effects and global treatment effect estimates should only be presented secondary to local treatment effect estimates.
- The relative efficiency compared to an adjusted analysis of the treatment effect in an RCT, was not dependent on the correlation between the treatment assignment variable and outcome since the adjustment affects the efficiency of an RCT as well.
- When designing a prospective RD study, we recommend researchers to use assignment variables that are feasible in clinical practice but do not necessarily have a high correlation with outcome, to facilitate patient inclusion and optimize efficiency in a prospective RD design.