General Introduction

Over the last decades treatment guidelines have increasingly been based on the best available scientific evidence. In the early 1990s(1) the concept of Evidence Based Medicine (EBM) was introduced as a systematic approach to analyse published research as the basis of clinical decision making. The implementation of EBM was taken up worldwide by the Cochrane Collaboration. The existing medical scientific literature, with special attention to randomized trials, was summarized in tightly protocolized systematic reviews, which were then widely distributed through the Cochrane Library.(2) In this framework, meta-analysis of randomized clinical trials (RCTs) are regarded as the gold standard to provide evidence of causal effectiveness of medical interventions.(3)

However, RCTs are increasingly criticised for several reasons. First, RCTs have strict inclusion criteria limiting the generalizability for the full population of patients. Moreover, financial, ethical, and practical constraints prevent RCTs from being conducted for all clinical questions to guide clinical decision-making.(4) Also, recruitment of sufficient numbers of patients is a challenge in RCTs. Patients' treatment preferences and clinicians' lack of perceived equipoise are often cited as barriers to recruitment in RCTs.(3, 5, 6)

Recently, comparative effectiveness research (CER) gained increasing attention as a method to deliver broadly generalizable evidence on effectiveness of interventions. CER is the direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and the least harms.(7) The core question of CER is which treatment works best, for whom, and under what circumstances.(7) CER is not using data from patients with random allocation of treatments as in an RCT, but may include pragmatic RCTs or observational data that represent the current practice of treatments in 'real life'. Partly due to the ample availability of observational data, there is increasing attention for observational and quasi-experimental study designs that can be applied in such data.

The most important methodological challenge in observational data, is to determine whether the medical intervention under study is causally related to an outcome, rather than simply being correlated with another factor that is truly causally related to the outcome under study.(3) This is a particular threat as in observational studies comparison groups are different because of non-random treatment allocation. Patients are treated in accordance to the preferences of treating physicians, rather than because of a coin flip, like in randomized studies.(8, 9) These treatment choices are frequently informed by a patient's severity of illness. The treatment may be associated with outcome but could be interfered by other factors like disease severity that are causally related to outcome. Thus, observational studies assessing the causal effect of treatments are at risk of obtaining incorrect results. This type of bias is called confounding by indication.(4) It has been suggested that among non-randomized study designs, the quasi-experimental regression discontinuity (RD) design mostly resembles an RCT and overcomes confounding

by indication.(10, 11) But the methodological properties of this alternative study design are still unclear, and methods to increase the validity and efficiency need to be studied.

Thus, both randomized and non-randomized studies, like the RD design, have challenges to overcome. In this thesis, methodological challenges in both randomized and non-randomized studies are addressed. The benefits of covariate adjustment and proportional odds analysis, two different methods to optimize the validity and reliability of treatment effect estimates from RTCs in heterogeneous diseases are studied. Also, the (in)efficiency and threats to the validity of the RD design to estimate treatment effects are examined.

Randomized controlled trials

An RCT is an experimental study design in which the treatment is randomly allocated to patients. Random allocation between treatment and control group in such a study design means that patients are allocated to the groups in such a way that each participating patient has an equal chance of being allocated to either the treatment group (receiving the treatment) or the control group (not receiving the treatment).(3) All factors that can influence the outcome are on expectation equally distributed to the treatment and control group. This means when a difference in outcome between the treatment- and control group is found, this can be directly attributed to the treatment under study. The most important strength of an RCT is this controlled assignment of treatment which gives a good understanding of the assignment mechanism.(10) The treated and untreated patients in an RCT are unconditionally exchangeable.(10) This makes it possible to draw causal inference between treatment and the outcome under study in RCTs.

Nevertheless, RCTs may be difficult to set up in health care in practice for several reasons. First, the increasing complexity of regulations and logistics to conduct an RCT has raised the costs dramatically.(3, 12) Second, in part because of the high costs of RCT, an increasing proportion of studies is initiated by pharmaceutical companies that may influence the independency of the study. Third, patients may already receive a standard treatment that cannot be withheld but may interfere with the effects of a new treatment. Fourth, treating physicians may be convinced that the new treatment is better than the standard treatment and consider it unethical to withhold the new treatment even is the efficacy has not been proven.(3, 6) In addition, patient may have strong opinions on the effectiveness or risks of new treatments and not be willing to participate in a randomization. Hence, recruitment of adequate numbers of patients may be difficult in RCTs. Failure to achieve recruitment goals limits statistical precision, leads to an increase of costs, and decreases the efficiency of a RCT.(13) Even when investigators enrol a sufficient number of participants, they rarely do so on schedule.(6, 14) In addition, low recruitment rates threaten the generalizability of the findings in RCTs. A strict selection of patients enrolled in trials may poorly represent the population of interest, which limits the external validity of the results of a trial.(15, 16)

Specific challenges of RCTs in heterogeneous and rare diseases

Besides these more general limitations of RCTs, specific challenges with regard to efficiency arise when conducting RCTs in rare diseases with to the small numbers of patients(17) and in heterogeneous populations(18). In such a scenario, different approaches can be used to optimize the design and analysis in an RCT.

Random treatment allocation in RCTs ensures that observed and unobserved patient characteristics on average are similar between treatment arms.(17) However, it does not ensure full balance in small trials.(17) Differences in baseline risk on outcome other than treatment may arise between the treatment- and control group, simply due to chance.(17) In diseases with large heterogeneity in pathogenesis and natural disease course, severity and outcome, small differences in baseline risk on outcome between the treatment arms may influence the estimation of the treatment effect. In part, this effect can be compensated by increasing the number of patients included in the RCT. As indicated before, the rate of inclusion of patients is already a critical factor in most RCTs, but even more challenging in rare diseases. Small trials are also subject to a greater chance of imbalance between treatment arms than large trials.(17) Furthermore, small RCTs in rare diseases can easily fail to detect treatment benefits, due to lack of statistical power.

Covariate adjustment and ordinal outcome analysis

Two approaches to optimize the design and analysis of an RCT to increase the statistical power and to adjust for imbalances are covariate adjustment and ordinal analysis. Both approaches have been applied successfully in various acute neurological diseases such as stroke and traumatic brain injury.(19-21)

Covariate adjustment is a statistical method that adjusts the treatment effect for baseline risk on poor outcome in the treatment and control arms. When the treatment arms are unbalanced, the unadjusted estimate of the treatment effect may be biased. In addition, covariate adjustment increases statistical power.(17, 18, 22) In order to adjust for covariates in RCTs, it is required to have good knowledge on the prognostic factors for outcome, as the gain in power from covariate adjustment is directly related to the predictive strength of the adjustment model.(23) Prediction research can provide information on which covariates are important to adjust for in the analysis of the treatment effect.

Ordinal analysis is an approach to analyse a full ordinal outcome scale instead of a dichotomized version. It is common in medical research to use a functional or clinical outcome scale consisting of more than two categories, but often the ordinal outcome scale is dichotomized into favorable or unfavorable outcome as primary outcome of a study. In ordinal analysis the outcome is not dichotomized but analysed as the full ordinal scale with proportional odds analysis, preventing loss of information that occurs

when dichotomizing outcome measures.(24) Both simulation studies and empirical validation studies in various fields have demonstrated that proportional odds analysis increases the statistical power of RCTs.(24-27)

Non-randomized studies

There is an increasing interest to use non-randomized and observational data to study the effectiveness of medical interventions, for example in the framework of comparative effectiveness research. However, in observational data, it is complicated to draw causal inference between treatment and outcome. The treated patients may be systematically different from the control patients. For example, physicians could treat more severely affected patients differently form less severely affected patients.(4, 28) The disease severity could influence the risk on outcome of interest and can thus be a confounder for the causal relation between treatment and outcome. When this confounder is unmeasured it is impossible to correct for it in the analysis. This can lead to bias in the treatment effect estimate. This type of bias is called confounding by indication.

Regression discontinuity design

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. The RD design is common in social sciences, and was introduced in public health and medicine in 1996.(29) RD has been evaluated in other fields(30-35), but the importance of studying the feasibility and robustness of this design in clinical settings has been noted.(36-38) It has been suggested that RD is the observational design that most resembles an RCT.(10, 11) 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. (Figure 1) E.g. all patients with a baseline cholesterol level 5 mmol/L may receive treatment (intervention group) and patients with a baseline cholesterol level below 5 mmol/L do not receive treatment (control group). Such treatment assignment closely resembles clinical practice especially when a standard treatment protocol is used and may thus facilitate easier recruitment of participants into a prospective, comparative study. 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 provide an opportunity to obtain unbiased causal treatment effect estimates, when an RCT is not feasible.(39) Moreover, it might be attractive to apply the RD design as a prospective study because the challenges of the randomization of patients are eluded. However, it is unclear whether the estimates from a quasi-experimental RD design might be different and substantially less efficient compared to an RCT.

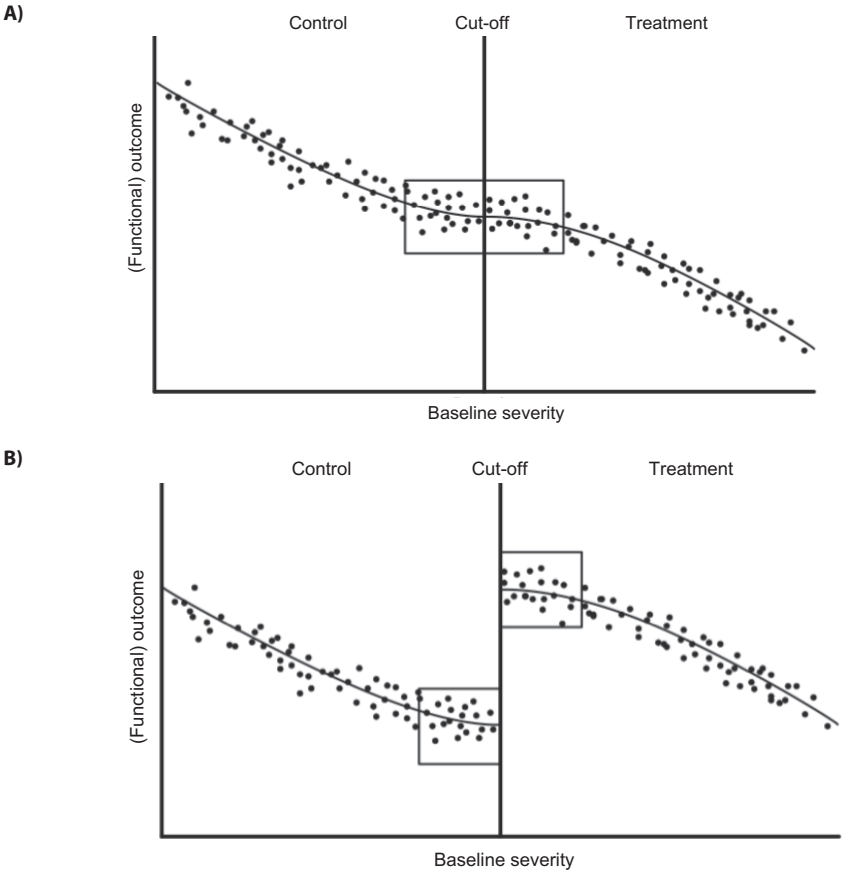

Figure 1. Graphical presentation of the regression discontinuity design in 2 studies showing no treatment effect (A) and showing a treatment effect (B).

Case-studies

The studies in this thesis test the different approaches to optimize the design and analysis of randomized and non-randomized studies in several databases on different neurological and cardio-vascular diseases.

Neurological diseases

Traumatic brain injury (TBI) is a serious public health problem with an estimated annual incidence of up to 500 cases per 100,000 population in the USA and Europe.(40-42) TBI is a major cause of death and disability, leading to great personal suffering for patients and relatives and huge direct and indirect costs to society.(40) It is defined as an injured brain as a result of an external force. TBI patients are variable with regard to causes, pathophysiology, treatment, and outcome.(40) Mild TBI patients may show full recovery, even without treatment. Severely affected TBI patients may develop serious psychologi-

cal and physical disabilities or die. A systematic literature search of the years from 1980 to 2009 revealed 27 large phase III trials in TBI; and at least further 6 unpublished trials.(43) Nevertheless, these clinical trials failed to show convincing efficacy of the treatments that were studied, mainly neuroprotective agents.(44-46) Currently the research efforts in TBI are shifting towards large observational studies to identify optimal effective treatments with CER.(47)

Guillain Barré Syndrome (GBS) is a life-threatening acute immune-mediated disorder of peripheral nerves and nerve roots (polyradiculoneuropathy)(48, 49) GBS requires early diagnosis and hospital admission for accurate monitoring, treatment and supportive care. Worldwide, the reported GBS incidence rates, vary between 0.4 and 4 per 100,000 per year, depending on age, sex, region, study methodologies and case ascertainment.(50) GBS is a heterogeneous disorder regarding pathogenesis, clinical presentation, severity and course and patients highly differ with respect to the required duration and intensity of hospital care.(51) Some patients with a mild form of GBS may show full recovery even without treatment. Other patients with a severe form of GBS may develop a full paralysis of the respiratory and limb muscles and require ventilation at an ICU for months despite treatment and may die or remain severely disabled. The current outcome of GBS is: a mortality rate of 5%, remaining unable to walk in 15% and the majority with residual complaints that interfere with daily life. In the last decade, various promising new immune-modulating treatments have been developed that may be effective in GBS as well but in this period only a very limited number of RCTs have been conducted in GBS worldwide. Because of these limitations, the treatment of GBS remained unchanged in the last 25 years.

Dementia is defined as significant loss of intellectual abilities, including memory, that is severe enough to interfere with social or occupational functioning. Increased life expectancy is associated with a steep increase of both the incidence and prevalence of dementia in the elderly. The number of 24.3 million patients that suffer from dementia is projected to almost double every 20 years to 81.1 million by the year 2040.(52, 53) Alzheimer disease is the most common cause of dementia, followed by vascular dementia.(52, 54) Treatment options for dementia are limited.(75, 76) Pharmaceutical treatment options include cholinesterase inhibitors, memantine and experimental medication. Cholinesterase inhibitors are only recommended for Alzheimer's disease and mixed dementia, not for vascular dementia or mild cognitive impairment. There is no proof of effectiveness for the other pharmaceutical options.(55) Future randomized and non-randomized studies should lead to both better prevention strategies and treatment possibilities and could help to decrease the burden of dementia.

Cardio-vascular diseases

Cardio-vascular disorders are also heterogeneous with regard to severity of symptoms, nature of clinical failure. An example of cardio-vascular diseases that is used in this thesis is acute myocardial infarction (MI). Acute MI, also known as a heart attack, is a major cause of morbidity and mortality worldwide. More than 3 million people each year are estimated to have an acute ST-elevation myocardial infarction (STEMI), with more than 4 million having a non-ST-elevation myocardial infarction (NSTEMI).(56) However, more effective treatment of patients hospitalized with acute myocardial infarction has led to a substantial decrease in deaths due to acute MI.(57) Several RCTs have established the beneficial effects and relative safety of several thrombolytic agents(58) (streptokinase(59, 60) tissue plasminogen activator(61)) and adjunctive medical therapy(62) (β-adrenergic antagonists(63), angiotensin-converting enzyme inhibitors).(64-67)

Studies used

For this thesis nine different datasets were used. An overview of the different studies, their description and in which chapters the datasets were used, is presented in Table 1.

Aim of the thesis

The aim of the thesis is to investigate how to optimize the design and analysis of randomized and non-randomized therapeutic studies, in order to increase the validity and reliability of causal treatment effect estimates, specifically in heterogeneous diseases.
The following research questions will be addressed:

1) What are the benefits of more advanced statistical analyses to estimate treatment effects from RTCs in heterogeneous diseases?
   a. What is the heterogeneity in acute neurological diseases with regard to baseline severity and further course of the disease?
   b. What is the potential gain in efficiency of covariate adjustment and proportional odds analysis in RCTs in Guillain-Barré syndrome (GBS)?
2) What is the validity and reliability of the RD design compared to an RCT to estimate causal treatment effects?
   a. What are threats to the validity of the RD design to estimate treatment effects compared to an RCT?
   b. How efficient is the RD design to estimate treatment effects compared to an RCT?
   c. What are the potential benefits of an alternative assignment approach in an RD design?

The thesis consists of two parts. In order to increase the validity and reliability in future RCTs in heterogeneous diseases, in part I (chapter 2, 3 and 4) the design and analysis of RCTs is studied. In chapter 2 the heterogeneity with regard to the current hospital

Table 1. Overview of datasets used in this thesis.

Abbreviation	Name	Disease	Description
PIV (68)	Pandemic Influenza & Vaccination study	GBS	The PIV study was originally designed to investigate the relation between GBS and the pandemic influenza A (H1N1) virus. Neurologists from all Dutch hospitals were requested to report patients diagnosed with GBS between November 2009 and November 2010.
PE vs IVIg trial (69)	Plasma Exchange (PE) vs Intravenous Immunoglobulin (IVIg) trial	GBS	The PE vs IVIg trial was a multicenter double-blind trial conducted between 1986 and 1989 and included 147 patients. The control group received IVIg and the treatment group received PE. The primary outcome was improvement by one or more grades on the GBS disability score after 4 weeks.
IVIg vs MP trial (70)	IVIg and placebo versus IVIg and Methyl-Prednisolone (MP) trial	GBS	In the IVIg vs MP trial, a multicenter double-blind trial, 225 patients were included between 1994 and 2000. The patients receiving IVIg and placebo were considered as control patients and the patients receiving IVIg and MP were considered as treated patients. The primary outcome was improvement by one or more grades on the GBS disability score after 4 weeks.
IMPACT (71)	International Mission on Prognosis and Clinical Trail design in TBI study	TBI	The IMPACT study combines individual patient data from 8 RCTs and three observational studies in moderate and severe TBI, mainly from the US and Europe. In Chapter 3 in this thesis we focused on the three observational studies (the European Brain Injury Consortium study (EBIC), the UK four center study (UK4), and the Traumatic Coma Databank (TCDB)). Patients were enrolled in these studies between 1984 and 1995.
CRASH (72)	Corticosteroid Randomisation After Significant Head injury trial	TBI	In the CRASH trial the effect of corticosteroids on death and disability after head injury was studied. CRASH enrolled 10,008 patients between 1999 and 2005. The primary outcome in CRASH was 14-day mortality.
TARN (73)	Trauma Audit & Research Network	TBI	TARN is a hospital based trauma registry in England and Wales including all patients with trauma resulting in immediate admission to hospital for three days or longer or death. The patients from TARN included in this study were enrolled between 1990 and 2009.
preDIVA (52)	Prevention of Dementia by Intensive Vascular Care study is	Vascular disease / dementia	An ongoing cluster-randomized trial to assess the efficacy of a multicomponent, nurse-led intervention targeting all cardiovascular risk factors in an elderly population (70-78 years). The primary outcome of this RCT is incident dementia during 6 years of follow-up. Of 3533 patients enrolled, 1894 are in the intervention and 1639 in the control group.
PROSPER (74)	PROspective Study of Pravastatin in elderly individuals at risk of vascular disease	Vascular disease	The study was conducted between December 1997 and May 1999 and enrolled 5804 patients, who were assigned to pravastatin (n=2891) or placebo (n=2913) to reduce the risk of coronary disease in elderly individuals. The outcome was a composite endpoint of coronary death, non-fatal myocardial infarction and fatal or non-fatal stroke at 3.2 years on average after randomization.

Table 1. (continued)

Abbreviation	Name	Disease	Description
GUSTO (61)	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries trial	Acute myocardial infarction	30,510 patients were entered between 1990 and 1993. 10,348 patients were assigned to treatment (accelerated tissue plasminogen activator) and 20,162 patients were used as control patients receiving streptokinase. The primary endpoint was 30-day mortality.

TBI = Traumatic Brain Injury, GBS = Guillain-Barré syndrome, RCTs = randomized controlled trials

admissions, transfers and costs in GBS is described (research question 1a). In chapter 3, also concerning research question 1a, a meta-analysis of the prognostic value of major extracranial injury in TBI patients is presented. Chapter 4 corresponds to research question 1b regarding the potential gain in efficiency of covariate adjustment and ordinal analysis in RCTs in GBS.

In part II (chapter 5, 6 and 7) the validity and reliability of the RD design compared to an RCT is addressed. Chapter 5 studies the validity and efficiency of the RD design in continuous outcomes. Similar research to chapter 5 is done in chapter 6, studying the validity and efficiency of the RD design in dichotomous outcomes. Chapter 7 focuses on the potential benefits of an alternative assignment approach to increase the efficiency of the RD design. The results of the studies in this thesis are further discussed in chapter 8, together with their implications.

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