Efficient design and analysis of randomized controlled trials in rare neurological diseases: an example in Guillain-Barré syndrome

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ABSTRACT

Introduction

Randomized controlled trials (RCTs) pose specific challenges in rare and heterogeneous neurological diseases due to the small numbers of patients and heterogeneity in disease course. Two analytical approaches have been proposed to optimally handle these issues in RCTs: covariate adjustment and ordinal analysis. We investigated the potential gain in efficiency of these approaches in rare and heterogeneous neurological diseases, using Guillain-Barré syndrome (GBS) as an example.

Methods

We analyzed two published GBS trials with primary outcome 'at least one grade improvement' on the GBS disability scale. We estimated the treatment effect using logistic regression models with and without adjustment for prognostic factors. The difference between the unadjusted and adjusted estimates was disentangled in imbalance (random differences in baseline covariates between treatment arms) and stratification (change of the estimate due to covariate adjustment). Second, we applied proportional odds regression, which exploits the ordinal nature of the GBS disability score. The standard error of the estimated treatment effect indicated the statistical efficiency.

Results

Both trials were slightly imbalanced with respect to baseline characteristics, which was corrected in the adjusted analysis. Covariate adjustment increased the estimated treatment effect in the two trials by 8% and 18% respectively. Proportional odds analysis resulted in lower standard errors indicating more statistical power.

Conclusion

Covariate adjustment and proportional odds analysis most efficiently use the available data and ensure balance between the treatment arms to obtain reliable and valid treatment effect estimates. These approaches merit application in future trials in rare and heterogeneous neurological diseases like GBS.

INTRODUCTION

RCTs are the standard to investigate the effectiveness of medical interventions. However, RCTs are challenging in rare heterogeneous diseases. The randomization process in RCTs ensures that observed and unobserved patient characteristics on average are similar between treatment arms.(1) However, it does not ensure full balance.(1) Different baseline risks for outcome can arise between treatment arms, simply due to chance.(1) In diseases with large between-patient differences in natural disease course, severity and outcome, small imbalances in covariates between the treatment arms may, positively or negatively, affect the estimated treatment effect.

Sample sizes in RCTs in rare diseases are usually small. Small trials are a subject to a greater chance of imbalance than large trials.(1)(Moreover, small RCTs can easily fail to detect treatment benefits, due to lack of statistical power. In rare neurological disorders, such as inflammatory neuropathies like Guillain-Barré syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN), this heterogeneity and rarity is a major challenge for conducting RCTs.

Two approaches to optimize RCT design and analysis that have been successfully applied in other acute neurological diseases such as stroke and traumatic brain injury are covariate adjustment and ordinal analysis.(2-4) (Table S1) Covariate adjustment is a statistical method that adjusts the treatment effect for baseline risk on poor outcome in the treatment arms. When the treatment arms are imbalanced, an unadjusted analysis is suboptimal to estimate the treatment effect. In addition, previous studies found that covariate adjustment could increase statistical power.(1, 5-9) Ordinal analysis is an approach to analyze a full ordinal outcome scale instead of a dichotomized version. Although these techniques already have been successfully applied in stroke and traumatic brain injury, it is still relevant to study this in other diseases like GBS, since the effect of the different approaches can work out differently in different study settings. The most commonly used outcome in GBS is the ordinal GBS disability score, consisting of seven categories. Usually the scale is dichotomized into favorable or unfavorable outcome, or the improvement on the GBS disability score from admission calculated and dichotomized as minimal one grade improvement. In ordinal analysis the outcome is not dichotomized but analyzed as the full ordinal scale with proportional odds analysis, preventing loss of information.(10) Simulation studies and empirical validation studies in other fields have demonstrated that proportional odds analysis increases statistical power in RCTs.(10-13)

To test the applicability and value of these approaches in rare and heterogeneous neurological diseases, we use Guillain-Barré syndrome (GBS) as an example. GBS is a life-threatening acute immune-mediated polyradiculoneuropathy(14, 15), which requires early diagnosis and hospital admission for accurate monitoring, treatment and

supportive care. Some patients may show spontaneous and full recovery, while others require ventilation at an ICU for months and remain severely disabled. Several RCTs have successfully been conducted in GBS.(16-18)

We aimed to explore the potential benefit of covariate adjustment and proportional odds analysis in rare and heterogeneous neurological diseases, compared to the conventional statistical approaches. We hereto re-analyzed two RCTs in GBS.

METHODS

Patient Population

We analyzed data from two RCTs in GBS, the Plasma Exchange (PE) vs Intravenous Immunoglobulin (IVIg) (PE vs IVIg) trial(17) and the IVIg and placebo versus IVIg and Methyl-Prednisolone (MP) (IVIg vs MP) trial(18), conducted between 1986 and 2000. In the PE vs IVIg trial, the control group received IVIg and the treatment group received PE. In the IVIg vs MP trial, 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 in both trials was improvement (corresponding to lower GBS disability scores) by one or more grades on the GBS disability score after 4 weeks. The GBS disability score is an ordinal scale ranging from 0 = healthy to 6 = dead. However, in order to estimate treatment effects for a positive outcome for all the analyses, we used the reversed GBS disability score at 4 weeks, to keep the estimates easy to compare. For all the regression models used in this paper, higher numbers (in outcome) mean better health outcomes.

Statistical analysis

The predicted probabilities for one grade improvement on the GBS disability score were calculated and used as a measure for baseline risk to indicate potential unbalance between the treatment arms in baseline characteristics.

To estimate treatment effects, we used two commonly used primary (dichotomous) outcomes in GBS trials as reference; (1) favorable outcome (0-2) on the GBS disability scale at 4 weeks as outcome and (2) minimal one grade improvement on the GBS disability score between the moment of randomization and 4 weeks as outcome, both analyzed with binary logistic regression without covariate adjustment. Consequently, these references were compared with the two approaches under study: covariate adjustment and ordinal analysis.

Covariate adjustment

With covariate adjustment, conditional treatment effects are estimated with regression models. Adjusting for GBS disability score at admission results in an estimated treatment effect for a patient with a given GBS disability score, while unadjusted analysis results in an average estimated treatment effect over all patients, irrespective of the GBS disability score. Unadjusted analysis is expressed by the following formula:

$$log\ odds\ (improvement) = \alpha + \beta * treatment,$$

where improvement is by one or more grades on the GBS disability score, and treatment is an indicator for the randomization arm. The coefficients α and β indicate the intercept and regression coefficient for treatment. In logistic regression, exp(β) indicates the odds ratio (OR).

For adjusted analysis, we used three well-known predictors of outcome(19, 20): age, preceding diarrhea and GBS disability score at admission. The covariate adjusted model is expressed by the following formula:

$$log\ odds\ (improvement) = \alpha + \beta * treatment + \beta 1 * age + \beta 2 * preceding\ diarrhea + \beta 3 * GBS\ disability\ score\ at\ admission.$$

This results in an adjusted regression coefficient β for the estimated treatment effect. In the trial analysis, the observed difference of the unadjusted and adjusted regression coefficient for the treatment variable is a result of imbalance and stratification.(8) We hereto calculated the linear predictor based on age, diarrhea and GBS disability score at admission. We then calculated the difference in treatment effect that was attributable to imbalance as the difference between the mean value of the linear predictor between the treatment arms.(8) The remaining part of the difference between the unadjusted and the adjusted treatment effect was attributed to stratified estimation, i.e. conditioning on covariates.(8)

Proportional odds analysis

For ordinal analysis we used proportional odds logistic regression to exploit the ordinal nature of the GBS disability score. A proportional odds logistic regression model was fitted with the GBS disability score collapsed to a 5-point scale. We combined both healthy (0) and minor symptoms (1), as well as needs ventilation at least a part of the day (5) and dead (6) because of small numbers in these extreme categories. We used the reversed GBS disability scale to estimate treatment effects on a positive outcome, and to keep these estimates comparable to the estimates of the other logistic regression models on positive dichotomous outcomes (improvement and favorable outcome). The proportional odds model uses an ordinal outcome variable with more than two possible categories. It estimates a common OR over all possible cut-offs of the outcome scale. Next, we used the difference between the GBS disability score at admission and the GBS

disability score at four weeks as outcome. A proportional odds logistic regression model was used to analyse the difference in GBS disability score.

Treatment effect estimates

The coefficient β of the treatment effect and the corresponding standard error (SE) were calculated for the four approaches to analyse outcome, with and without covariate adjustment. The SE of the treatment effect indicates the precision of the calculated treatment effect. The SEs in the proportional odds regression models are expected to be smaller than those in the logistic models. Both trials were analysed with complete case analysis, ignoring 1 and 4 patients with incomplete baseline data. Statistical analyses were performed in R Statistical Software version 2.15.3 using the rms package (R Foundation for Statistical Computation, Vienna, Austria).

RESULTS

Patient population and reference strategies

We analysed data from 146 patients in the PE vs IVIg trial and 221 patients in the IVIg vs IVIg+MP trial. Both trials were slightly imbalanced with regard to the baseline characteristics. In the IVIg vs IVIg+MP trial the treatment group (with MP) had a probability of 0.60 to improve at least one grade on the GBS disability score compared to a predicted probability of 0.64 in the control group (without MP). So without any treatment, the prognosis of the treatment arm was slightly better. An opposite distribution of baseline covariates between treatment arms is shown in the PE vs IVIg trial. The treatment group (PE) has a higher predicted probability (0.45) to improve at least one grade on the GBS disability score compared to the control group (IVIg; predicted probability 0.41, Table 1).

Regarding the actual outcome, 63 (57%) control patients treated with IVIg and placebo and 74 (67%) patients treated with IVIg and methylprednisolone improved minimal one grade on the GBS disability score after 4 weeks. In the other trial, 25 (34%) control patients treated with IVIg and 38 (52%) patients receiving PE improved minimal one grade on the GBS disability score after 4 weeks (Appendix 1).

The treatment under study in both trials had a positive effect on health outcomes. With the reference strategy of logistic regression on a favorable GBS disability scale (0 – 2) at 4 weeks as outcome, the estimated treatment OR was 1.80 (95% confidence interval (CI) 0.84 – 3.85, SE 0.39, p = 0.13) in the PE vs IVIg trial and 1.69 (95% CI 0.93 – 3.08, SE 0.31, p = 0.09) in the IVIg vs IVIg+MP trial. The treatment effect estimates on one grade improvement were slightly larger (Table 2).

Table 1. Distribution of baseline predictors and outcome distribution in two randomized controlled trials in GBS.

	PE vs IVIg trial			IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial		
	Total (n = 146)	**Control (PE) (n =73)**	**Treatment (IVIg) (n = 73)**	**Total (n = 221)**	**Control (IVIg) (n = 111)**	**Treatment (IVIg+MP) (n = 110)**
Age (Median, Interquartile Range 25th-75th Percentile)	49 (32 – 63)	51 (33 – 66)	47 (32 – 61)	55 (35 - 67)	52 (35 – 67)	57 (34 – 68)
Preceding diarrhea	27 (19%)	16 (22%)	11 (15%)	60 (27%)	30 (27%)	30 (27%)
GBS disability score at admission						
Able to walk over 10m open space with help	29 (20%)	16 (22%)	13 (18%)	58 (26%)	32 (30%)	26 (24%)
Bedridden or chair bound	92 (63%)	44 (60%)	48 (66%)	153 (49%)	78 (70%)	75 (68%)
Needs ventilation for at least a part of the day	25 (17%)	13 (18%)	12 (16%)	10 (5%)	1 (1%)	9 (8%)
Predicted probability of one or more grades improvement on the GBS disability score after 4 weeks	0.43	0.41	0.45	0.62	0.64	0.60
One or more grades improvement on the GBS disability score after 4 weeks	63 (43%)	25 (34%)	38 (52%)	137 (62%)	63 (57%)	74 (67%)
GBS disability score after 4 weeks						
0 = Healthy	0 (0%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)	5 (5%)
1 = Minor symptoms	16 (11%)	6 (8%)	10 (14%)	37 (17%)	24 (22%)	13 (12%)
2 = Able to walk 10m unassisted but not able to run	30 (21%)	12 (16%)	18 (25%)	74 (34%)	31 (28%)	43 (39%)
3 = Able to walk over 10m open space with help	19 (13%)	9 (12%)	10 (14%)	22 (10%)	10 (9%)	12 (11%)
4 = Bedridden or chair bound	48 (33%)	27 (37%)	21 (29%)	54 (24%)	31 (28%)	23 (21%)
5 = Needs ventilation for at least a part of the day	31 (21%)	17 (23%)	14 (19%)	26 (12%)	14 (13%)	12 (11%)
6 = Dead	2 (1%)	2 (3%)	0 (0%)	3 (1%)	1 (1%)	2 (2%)

Table 2. Treatment effect analysis: unadjusted and adjusted binary and proportional odds logistic regression.

		PE vs IVIg trial (n = 146)		IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (n = 221)	
		Unadjusted	Adjusted*	Unadjusted	Adjusted*
Binary logistic regression – GBS disability 3-6 vs 0-2 **	OR (95% CI)	1.90 (0.93 – 3.87)	1.80 (0.84 – 3.85)	1.27 (0.75 – 2.15)	1.69 (0.93 – 3.08)
	SE	0.36	0.39	0.27	0.31
	P-value	0.08	0.13	0.38	0.09
Binary logistic regression – improvement on GBS disability score	OR (95% CI)	2.08 (1.07 – 4.06)	1.95 (0.96 – 4.00)	1.57 (0.91 – 2.71)	1.96 (1.08 – 3.56)
	SE	0.34	0.36	0.28	0.31
	P-value	0.03	0.06	0.11	0.03
Proportional odds logistic regression – reversed GBS disability score at 4 weeks**	OR (95% CI)	1.76 (0.98 – 3.19)	1.76 (0.98 – 3.19)	1.12 (0.70 – 1.80)	1.41 (0.87 – 2.28)
	SE	0.30	0.30	0.24	0.25
	P-value	0.06	0.06	0.63	0.17
Proportional odds logistic regression – Δ GBS disability score (grades improvement between admission and 4 weeks)	OR (95% CI)	1.93 (1.07 – 3.49)	1.80 (0.99 – 3.27)	1.43 (0.89 – 2.30)	1.34 (0.89 – 2.32)
	SE	0.30	0.30	0.24	0.25
	P-value	0.03	0.05	0.14	0.14

**Adjustment for age, preceding diarrhea and GBS disability score at admission. ** 0 = Healthy / 1 = Minor symptoms / 2 = Able to walk 10m unassisted but not able to run / 3 = Able to walk over 10m open space with help / 4 = Bedridden or chair bound / 5 = Needs ventilation for at least a part of the day / 6 = Dead*

*** In order to estimate the treatment effect for a positive outcome, we used the reversed GBS disability score at 4 weeks*

Covariate adjustment

With covariate adjustment, the estimated treatment effect was larger in the IVIg vs IVIg+MP trial, partly as a result of adjustment, which makes the estimates more extreme, and partly because of the imbalance at baseline. Poorer prognosis at baseline for the intervention (IVIg + MP) group implied a +31% increase in the adjusted treatment effect (Table 3). The stratification effect of adjustment was an additional 18% increase in the treatment effect (OR = 1.96). In contrast, the treatment effect was smaller with adjustment for baseline characteristics in the PE vs IVIg trial. The stratification effect increased the treatment effect with 8%, but the better prognosis in the intervention (IVIg) group at baseline reduced the estimated treatment effect by -24%. The net effect was a difference in treatment effect of -16%. These results were similar for all binary and ordinal outcome analyses (Table 2).

Table 3. Results of unadjusted and adjusted binary logistic regression analysis of the effect of treatment versus control on GBS disability score at four weeks in both PE vs IVIg trial (n = 146) and the IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (n = 221).

	OR	Coefficient	Absolute difference in treatment effect between adjusted and unadjusted	Imbalance between treatment arms	Relative difference in treatment effect between adjusted and unadjusted due to imbalance	Relative difference in treatment effect between adjusted and unadjusted due to stratification
			PE vs IVIg trial			
Unadjusted	2.08	0.73				
Adjusted for age, preceding diarrhea and GBS disability score at admission	1.95	0.67	- 0.06^	-0.12	-16%*	8%#
			IVIg vs MP trial			
Unadjusted	1.57	0.45				
Adjusted for age, preceding diarrhea and GBS disability score at admission	1.96	0.67	0.22^	0.14	31%*	18%#

^ *Adjusted coefficient – Unadjusted coefficient*

* *Imbalance between treatment arms / Unadjusted coefficient*

(Absolute difference in treatment effect between adjusted and unadjusted - Imbalance between treatment arms) / Unadjusted coefficient

Proportional odds analysis

For illustration of the proportional odds analyses we calculated the treatment effect estimates (ORs) for each cut-off of the reversed ordinal scale. The common OR can be interpreted as the pooled estimate of these binary ORs. The treatment under study in both trials had a positive effect on health outcomes in all the ordinal analyses. In the PE vs IVIg trial the ORs over each cut-off were relatively similar (Figure 1c and 1d). The common OR was similar as well, but the SE and CI were smaller. In the IVIg vs IVIg+MP trial, the ORs were more variable (Figure 1a and 1b). The common OR was less extreme compared to ORs for the cut-off used in the reference approach (0-2 vs. 3-6 and minimal one grade improvement vs. no improvement). But again, the SE and CI were smaller. This can also be seen in table 2; in all analyses, the proportional odds analysis on the GBS disability score after four weeks and on the improvement on the GBS disability score resulted in lower SEs of the treatment effect compared to the binary approaches.

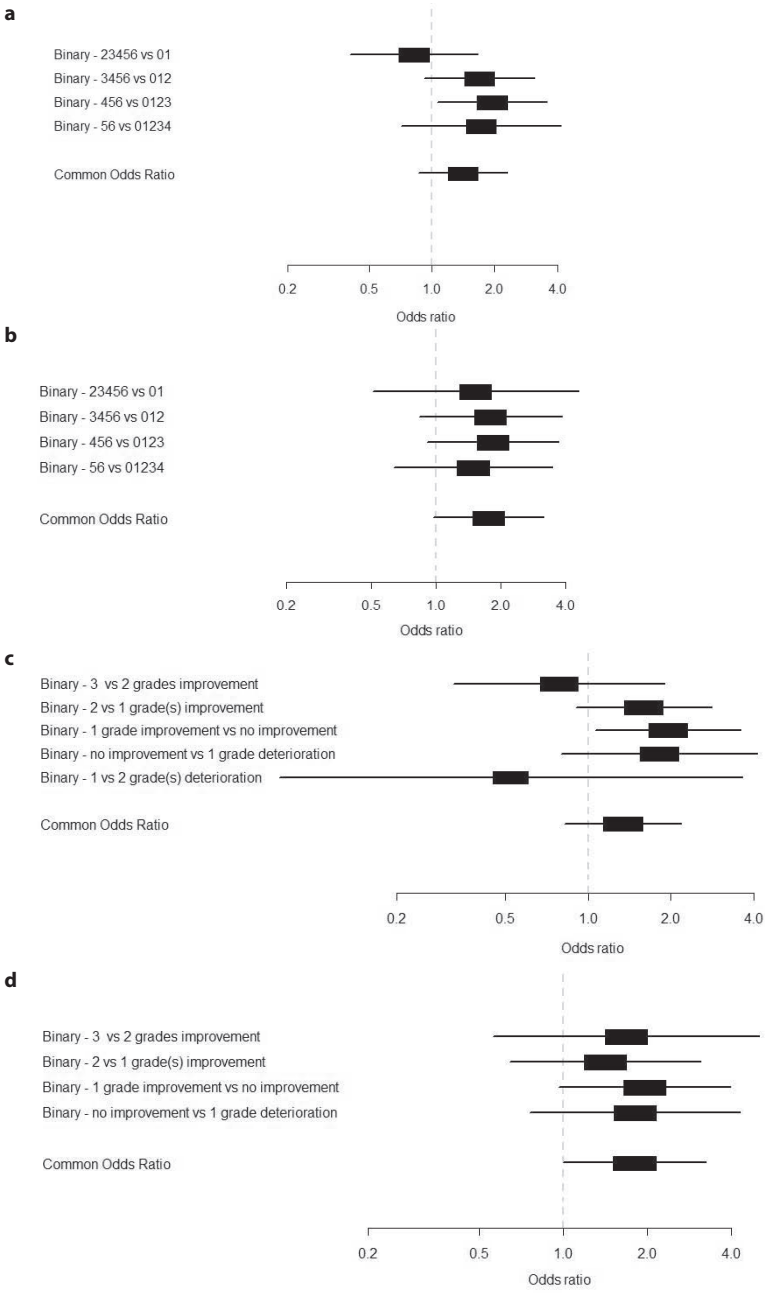


Figure 1. Treatment effect analysis: forest plots of the adjusted binary and proportional odds logistic regression in the IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (a and b) and PE vs IVIg trial (c and d) show smaller confidence intervals for the common odds ratio compared to the binary estimates.

Table 4. Characteristics of four methods of treatment effect analysis in GBS trials. Approach in BOLD is the recommended approach.

	Takes into account baseline imbalance	**Takes into account ordinal nature of the outcome measure**
Unadjusted binary logistic regression on cutoff for GBS disability score	NO	NO
Adjusted binary logistic regression on cutoff for GBS disability score	YES	NO
Unadjusted binary logistic regression on ≥ 1 grade improvement on GBS disability score	PARTLY*	NO
Adjusted binary logistic regression on ≥ 1 grade improvement on GBS disability score	YES	NO
Unadjusted proportional odds logistic regression on GBS disability score	NO	YES
Adjusted proportional odds logistic regression on GBS disability score	**YES**	**YES**
Unadjusted proportional odds logistic regression on Δ GBS disability score	PARTLY*	YES
Adjusted proportional odds logistic regression on Δ GBS disability score	YES	YES

*Only baseline GBS disability score, no other covariates

DISCUSSION

In this study we assessed the potential benefit of the use of covariate adjustment and proportional odds analysis in RCTs compared to the conventional method, by reanalyzing two GBS trials. We found that covariate adjustment increased the estimated treatment effect in one trial, and decreased the estimated treatment effect in the other trial, due to imbalances in baseline characteristics between the treatment arms. Although such imbalances are fully due to chance if a proper randomization procedure is followed, our results illustrate that their impact on interpretability of treatment effect estimates can be substantial and can be different in several study settings. We found that the proportional odds analysis resulted in lower standard errors and thus smaller confidence intervals of the treatment effect estimate compared to the conventional method of logistic regression on dichotomized outcome measures. Thus, dichotomization of ordinal outcome measures does not merit application. In future trials in rare and heterogeneous neurological diseases like GBS both covariate adjustment and proportional odds analysis are advised.

Covariate adjustment

On expectation, covariate adjustment leads to more extreme treatment effect estimates and larger standard errors for non-linear regression models.(21) The p values are a function of the treatment effect estimates and standard error. With covariate adjustment the increase in treatment effect estimate will outweigh increased in standard error and the p values will be lower compared to unadjusted analysis.(21)

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 PE vs IVIg trial. In the 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.

Covariate adjustment increases statistical power, despite the larger standard error.(1, 7) When there are no baseline imbalances, the adjusted conditional estimates will be more extreme than the unadjusted marginal estimates.(22) However, the size and the direction of the difference between the unadjusted and adjusted estimates are dependent on the strength of the prognostic factors and the imbalance in baseline risk between the treatment- and control group in the specific trial and this is shown in our study. When investigating the effectiveness of a medical intervention in rare and heterogeneous neurological diseases, such as GBS, one has to deal with small sample sizes. We therefore recommend performing covariate adjustment in future trials in rare and heterogeneous neurological diseases. For GBS this covariate adjustment should be applied with known predictors for (functional) outcome, specifically age, preceding diarrhea, GBS disability score and MRC sum score.(19, 20)

The outcome 'minimal one grade improvement' implicitly involves a form of covariate adjustment. The baseline disease severity of the patient is taken into account in the analysis by estimating improvement for each patient from his or her own starting position at admission (Table 4). This principle of a measure of change between baseline and follow up seems attractive to control for baseline imbalance. However, analyzing change does not control for baseline imbalance because of regression to the mean;(23, 24) baseline values are negatively correlated with change because patients with high scores at baseline generally improve more than those with low scores.(25) Therefore covariate adjustment with the absolute baseline value is still preferable over implicitly taking into account baseline severity in the outcome measure 'improvement'. Moreover, disease severity at baseline is not the only covariate we could adjust for. Especially, the age of the patient will be an important covariate in most neurological diseases.

Thus, in general, ignoring baseline imbalance between treatment arms in trials may cause invalid conclusions on both the magnitude and significance of the treatment effect estimate compared to analysis using covariate adjustment. The impact on interpretability of treatment effect estimates can be substantial and can be different in several study

settings. When designing a trial, the analysis plan should be precisely pre-specified. Also, the covariates that will be used for adjustment should be pre-specified. Previous studies have shown that the stronger the relation of the covariates with outcome, the larger the increase in statistical power with covariate adjustment will be.(5, 26, 27) In GBS, predictors of outcome are relatively well known(19, 20) and therefore pre-specifying important baseline variables for covariate adjustment is possible in GBS trials.

Proportional odds analysis

It is evident that the GBS disability scale is not a linear scale. For example, improvement from "needs ventilation for at least a part of the day" to "bedridden or chair bound" is not the same improvement as the improvement from "able to walk over 10m open space with help" to "able to walk 10m unassisted but not able to run". However, whether or not the ordinal outcome under study is a linear scale is not relevant for the validity of the proportional odds analysis. Proportional odds analysis merely requires ordering of outcomes. The proportional odds analysis estimates the treatment effect on each cut-off of the scale, instead of estimating the treatment effect on the difference between the averages scores in the treatment arms, as linear regression. The proportional odds model results in a common OR, which is interpretable as a pooled OR over all ORs for the different cut-offs. The common OR is formally valid if the ORs for each cut-off are the same (the proportional odds assumption). We can, however, interpret the common OR as a summary measure of the treatment effect, even if the ORs differs slightly per cut-off.(12, 28) The common OR can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study.(10-13) Moreover, simulation studies have shown that ordinal analysis is more efficient than binary analysis, even if the proportional odds assumption is violated.(11) 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. Although the importance of applying proportional odds analysis already has been assessed in other diseases, it is still relevant to study this for specific cases like GBS. For example it is important to have more insight in the effect of treatment on the different cut-offs for the specific ordinal outcome measure, in this case the GBS disability score, and see if the proportional odds assumption holds.

In the PE vs IVIg trial, the ORs for each cut-off were very similar and as a result the common OR was also similar. Thus, with the smaller SE, the p value was lower. In contrast, in the IVIg vs IVIg+MP trial, the ORs were more scattered. One explanation is chance: the ORs for the different cut-offs are uncertain, especially at the tails of the outcome scale where numbers are usually small. However, almost all binary ORs have confidence intervals that overlap. Another explanation is that the effect is truly different for different

cut-offs, although this is clinically unlikely. The cut-off chosen in the reference approach in the analysis of improvement appeared to be the most optimal cut-off from a statistical perspective, since it was the only cut-off resulting in a significant treatment effect.

However, if we assume a relatively constant treatment effect across the different cut-offs of an ordinal outcome scale, it is unpredictable which cut-off will show the strongest effect. Therefore, the ordinal analysis is a 'safe' choice and the common OR is a fair representation of the effect of treatment on the ordinal outcome compared to the binary approach, because it takes into account improvement over all levels of the GBS disability score. Since it is also more efficient, we recommend the use of the full ordinal outcome scale in future trials in rare and heterogeneous neurological diseases. In observational studies, ordinal analyses could be combined with propensity score methods to maximize statistical power.

Limitations

Patients with missing covariate data were excluded from the analyses. Data from 367 patients were analyzed rather than 372 patients in the original analyses. We did not assess heterogeneous treatment effects according to baseline risk, which could influence the ability of covariate adjustment to improve the statistical power in an RCT. In this study we only investigated GBS which may not fully be representative for other neurological disorders, although covariate adjustment and proportional odds analysis have shown advantages in other fields, such as stroke and traumatic brain injury.(3, 4, 7, 12)

Conclusion and implications

Covariate adjustment corrects for baseline imbalance and increases power. Proportional odds analysis optimally exploits the ordinal nature of outcome scales. A combined approach is advised for reliable and efficient estimation of treatment effects in small RCTs in rare and heterogeneous diseases like GBS.

REFERENCES

1. Thompson DD, Lingsma HF, Whiteley WN, Murray GD, Steyerberg EW. Covariate adjustment had similar benefits in small and large randomized controlled trials. J Clin Epidemiol. 2015;68(9):1068-75.
2. Maas AI, Steyerberg EW, Marmarou A, McHugh GS, Lingsma HF, Butcher I, et al. IMPACT recommendations for improving the design and analysis of clinical trials in moderate to severe traumatic brain injury. Neurotherapeutics. 2010;7(1):127-34.
3. Optimising Analysis of Stroke Trials C, Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. Stroke. 2007;38(6):1911-5.
4. Optimising the Analysis of Stroke Trials C, Gray LJ, Bath PM, Collier T. Should stroke trials adjust functional outcome for baseline prognostic factors? Stroke. 2009;40(3):888-94.
5. Hernandez AV, Steyerberg EW, Butcher I, Mushkudiani N, Taylor GS, Murray GD, et al. Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. J Neurotrauma. 2006;23(9):1295-303.
6. Hernandez AV, Steyerberg EW, Habbema JD. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. J Clin Epidemiol. 2004;57(5):454-60.
7. Roozenbeek B, Maas AI, Lingsma HF, Butcher I, Lu J, Marmarou A, et al. Baseline characteristics and statistical power in randomized controlled trials: selection, prognostic targeting, or covariate adjustment? Crit Care Med. 2009;37(10):2683-90.
8. Steyerberg EW, Bossuyt PM, Lee KL. Clinical trials in acute myocardial infarction: should we adjust for baseline characteristics? Am Heart J. 2000;139(5):745-51.
9. Turner EL, Perel P, Clayton T, Edwards P, Hernandez AV, Roberts I, et al. Covariate adjustment increased power in randomized controlled trials: an example in traumatic brain injury. J Clin Epidemiol. 2012;65(5):474-81.
10. Valenta Z, Pitha J, Poledne R. Proportional odds logistic regression--effective means of dealing with limited uncertainty in dichotomizing clinical outcomes. Stat Med. 2006;25(24):4227-34.
11. McHugh GS, Butcher I, Steyerberg EW, Marmarou A, Lu J, Lingsma HF, et al. A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: results from the IMPACT Project. Clin Trials. 2010;7(1):44-57.
12. Roozenbeek B, Lingsma HF, Perel P, Edwards P, Roberts I, Murray GD, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. Crit Care. 2011;15(3):R127.
13. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke. 2007;38(11):3055-62.
14. Hughes RA, Cornblath DR. Guillain-Barre syndrome. Lancet. 2005;366(9497):1653-66.
15. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis. 1997;176 Suppl 2:S92-8.
16. Garssen MP, van Koningsveld R, van Doorn PA, Merkies IS, Scheltens-de Boer M, van Leusden JA, et al. Treatment of Guillain-Barre syndrome with mycophenolate mofetil: a pilot study. J Neurol Neurosurg Psychiatry. 2007;78(9):1012-3.
17. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. N Engl J Med. 1992;326(17):1123-9.

18. van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA, et al. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. Lancet. 2004;363(9404):192-6.
19. van Koningsveld R, Steyerberg EW, Hughes RA, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barre syndrome. Lancet Neurol. 2007;6(7):589-94.
20. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology. 2011;76(11):968-75.
21. Robinson LD, Jewell NP. Some Surprising Results about Covariate Adjustment in Logistic Regression Models. International Statistical Review / Revue Internationale de Statistique. 1991;59(2):227-40.
22. Hauck WW, Neuhaus JM, Kalbfleisch JD, Anderson S. A consequence of omitted covariates when estimating odds ratios. J Clin Epidemiol. 1991;44(1):77-81.
23. Bland JM, Altman DG. Regression towards the mean. BMJ. 1994;308(6942):1499.
24. Bland JM, Altman DG. Some examples of regression towards the mean. BMJ. 1994;309(6957):780.
25. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323(7321):1123-4.
26. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet. 2000;355(9209):1064-9.
27. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med. 2002;21(19):2917-30.
28. Senn S. A random effects model for ordinal responses from a crossover trial. Stat Med. 1993;12(22):2147-51.
29. Hernandez AV, Steyerberg EW, Taylor GS, Marmarou A, Habbema JD, Maas AI. Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: a systematic review. Neurosurgery. 2005;57(6):1244-53; discussion -53.
30. Ciolino J, Zhao W, Martin R, Palesch Y. Quantifying the cost in power of ignoring continuous covariate imbalances in clinical trial randomization. Contemp Clin Trials. 2011;32(2):250-9.
31. Ciolino JD, Martin RH, Zhao W, Jauch EC, Hill MD, Palesch YY. Covariate imbalance and adjustment for logistic regression analysis of clinical trial data. J Biopharm Stat. 2013;23(6):1383-402.
32. Garofolo KM, Yeatts SD, Ramakrishnan V, Jauch EC, Johnston KC, Durkalski VL. The effect of covariate adjustment for baseline severity in acute stroke clinical trials with responder analysis outcomes. Trials. 2013;14:98.
33. Senn S, Julious S. Measurement in clinical trials: a neglected issue for statisticians? Stat Med. 2009;28(26):3189-209.
34. Diaz I, Colantuoni E, Rosenblum M. Enhanced precision in the analysis of randomized trials with ordinal outcomes. Biometrics. 2016;72(2):422-31.

Table S1. Overview of a selection of methodological studies considering covariate adjustment and ordinal analysis in RCTs.

First author	Year	Field	Key findings and conclusions
Covariate adjustment			
Robinson(21)	1991	-	In classic linear regression, the adjustment for a non-confounding predictive covariate, results in improved precision, whereas such adjustment in logistic regression results in a loss of precision. However, when testing for a treatment effect in randomized studies, it is always more efficient to adjust for predictive covariates when logistic models are used, and thus in this regard the behavior of logistic regression is the same as that of a classic linear regression.
Hauck(22)	1991	-	In the epidemiologic literature, one finds three criteria for confounding, which we will call the classical (marginal), operational (change-in-estimate) and conditional criteria. We define mavericks to be covariates that satisfy the operational criterion, but not the classical criterion. We present what is known about the problems of mavericks for estimating odds ratios and clarify the interpretation of oddsratios. Key results are: (1) omitting mavericks biases odds ratios towards 1; (2) omitting mavericks cannot artificially introduce an effect in contrast to omitting classical confounders; (3) the operational criterion for confounding corresponds to the conditional criterion when estimating odds ratios, but for relative risks, there are no mavericks (i.e. the classical and operational criterion correspond); and (4) the interpretation of odds ratios obtained from standard methods is that of comparing proportions, not of individual risk.
Pocock(27)	2002	-	When reporting the trial's findings baseline data can be used for i.a. covariate-adjusted analyses which aim to refine the analysis of the overall treatment difference by taking account of the fact that some baseline characteristics are related to outcome and may be unbalanced between treatment groups and baseline comparisons which compare the baseline characteristics of patients in each treatment group for any possible differences. This paper examines how these issues are currently tackled in the medical journals, based on a recent survey of 50 trialreports in four major journals. Key issues include: inconsistencies in the use of covariate-adjustment; the lack of clear guidelines on covariate selection; the overuse of baseline comparisons in some studies; the misuses of significance tests for baseline comparability, and the need for trials to have a predefined statistical analysis plan for all these uses of baseline data.
Hernandez(6)	2004	-	Logistic regression analysis was applied to simulated data sets (n=360) with different treatment effects, covariate effects, outcome incidences, and covariate prevalence. Treatment effects were estimated with or without adjustment for a single dichotomous covariate. The power was highest with prespecified adjustment. The potential reduction in sample size was higher with stronger covariate effects (from 3 to 46%, at 50% outcome incidence and covariate prevalence) and independent of the treatment effect. At lower outcome incidences and/ or covariate prevalence, the reduction was lower.

Table S1. Overview of a selection of methodological studies considering covariate adjustment and ordinal analysis in RCTs. (continued)

First author	Year	Field	Key findings and conclusions
Hernandez(29)	2005	Traumatic brain injury	18 RCTs (n = 6439) were identified in a systematic review of therapeutic phase III RCTs, including adult patients with acute, moderate-to-severe TBI to assess actual reporting of covariate adjustment according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations. Five RCTs reported covariate adjustment. The number of covariates was limited (<=5), most frequently including age. Many covariates were outcome predictors. Four RCTs reported only adjusted treatment effects as the main efficacy parameter. The reported covariate adjustment in TBI trials had several methodological shortcomings. Appropriate performance and reporting of covariate adjustment and subgroup analysis should be considerably improved in future TBI trials because interpretation of treatment benefits may be misleading otherwise.
Hernandez(5)	2006	Traumatic brain injury	Individual patient data from seven therapeutic phase III randomized clinical trials (RCTs; n = 6166) in moderate or severe TBI, and three TBI surveys (n = 2238) were used to calculate the potential sample size reduction obtained by adjustment of a hypothetical treatment effect for one to seven predictors with logistic regression models. The distribution of predictors was more heterogeneous in surveys than in trials. Adjustment of the treatment effect for the strongest predictors (age, motor score, and pupillary reactivity) yielded a reduction in sample size of 16-23% in RCTs and 28-35% in surveys. Adjustment for seven predictors yielded a reduction of about 25% in most studies: 20-28% in RCTs and 32-39% in surveys.
Optimizing the Analysis of Stroke Trials (OAST) Collaboration(5)	2009	Acute stroke	Data from 23 stroke trials (N = 25 674) assessing functional outcome were included. Unadjusted and adjusted ordinal logistic regression models were compared using simulated data from each trial (10 000 simulations per trial). Three levels of treatment effect were assessed with ORs of 0.95, 0.74, and 0.57. Adjusting for prognostic factors in stroke trials can reduce sample size by at least 20% to 30% (the lower interquartile range) for a given power and is similar across all 3 treatment effects
Roozenbeek(7)	2009	Traumatic brain injury	Statistical modeling studies in three surveys and six randomized controlled trials were performed using individual patient data from the IMPACT database. Covariate adjustment reduced sample sizes by 30% in surveys and 16% in RCTs. Covariate adjusted analysis in a broadly selected group of patients is advisable if a uniform treatment effect is assumed, since there is no decrease in recruitment.
Steyerberg(8)	2010	Acute myocardial infarction	The effects of adjustment (correction for imbalance and stratification) were studied with logistic regression analysis in the GUSTO-I trial. When adjusted for 17 characteristics, the odds ratio was 0.820, an increase of 25% compared to the unadjusted odds ratio. The increase in effect estimate was largely explained by the stratification effect and only partly by imbalance of predictors. Adjustment for predictive baseline characteristics, even when largely balanced, may lead to clearly different estimates of the treatment effect on mortality rates.

Table S1. Overview of a selection of methodological studies considering covariate adjustment and ordinal analysis in RCTs. (continued)

First author	Year	Field	Key findings and conclusions
Ciolino(30)	2011	Acute ischemic stroke	Based on data from a clinical trial of acute ischemic stroke treatment, computer simulations were used to create scenarios varying from the best possible baseline covariate balance to the worst possible imbalance, with multiple balance levels between the two extremes. Our simulation results show that the worst possible imbalance is highly unlikely, but it can still occur under simple random allocation. Also, power loss could be nontrivial if balancing distributions of important continuous covariates were ignored even if adjustment is made in the analysis for important covariates. This situation, although unlikely, is more serious for trials with a small sample size and for covariates with large influence on primary outcome.
Turner(9)	2012	Traumatic brain injury	14-day mortality was analyzed in 9,497 TBI patients in the CRASH trial of corticosteroid vs.placebo. Adjustment was made using logistic regression for baseline covariates of two validated risk models (IMPACT and CRASH) derived from external data. The relative sample size (RESS) measure, defined as the ratio of the sample size required by an adjusted analysis to attain the same power as the unadjusted reference analysis, was used to assess the impact of adjustment. RESS of 0.79 and 0.73 were obtained by adjustment using the IMPACT and CRASH models, respectively, which, for example, implies an increase from 80% to 88% and 91% power, respectively.
Ciolino(31)	2013	Acute stroke	This article uses simulation to quantify the benefit of covariate adjustment in logistic regression. Results suggest that if adjustment is not possible or unplanned in a logistic setting, balance in continuous covariates can alleviate some (but never all) of the shortcomings of unadjusted analyses.
Garofolo(32)	2013	Acute stroke	Using a current stroke clinical trial and its pilot studies to guide simulation parameters, 1,000 clinical trials were simulated at varying sample sizes under several treatment effects to assess power and type I error. Covariate-adjusted and unadjusted logistic regressions were used to estimate the treatment effect under each scenario. Under various treatment effect settings, the operating characteristics of the unadjusted and adjusted analyses do not substantially differ. Power and type I error are preserved for both the unadjusted and adjusted analyses.
Thompson(1)	2015	Stroke and acute myocardial infarction	In two large trial data sets GUSTO-I (N = 30,510) and IST (N = 18,372) random samples (500,000 times) of sizes 300 and 5,000 per arm were repeatedly drawn, and simulated each primary outcome using the control arms. The power gained from a covariate adjusted analysis for small and large samples was between 5% and 6%. Similar proportions of discordance with respect to statistical significance were noted irrespective of the sample size in both the GUSTO-I and the IST data sets.
Ordinal outcome analysis			

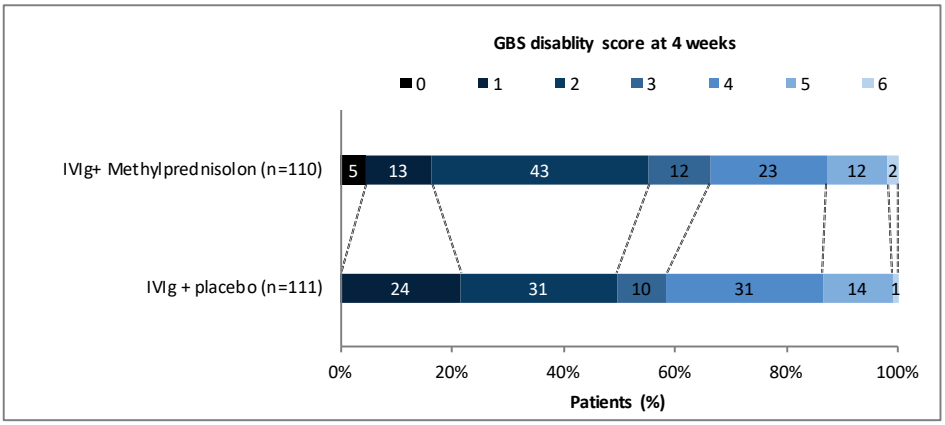
Table S1. Overview of a selection of methodological studies considering covariate adjustment and ordinal analysis in RCTs. (continued)

First author	Year	Field	Key findings and conclusions
Valenta(10)	2006	-	In this article conceptual and methodological aspects of employing proportional odds logistic regression for a three level ordinal factor as a suitable alternative to ordinary logistic regression when dealing with limited uncertainty in classifying clinical outcome as a binary variable are reviewed. Classifying a measurable clinical outcome as a dichotomous variable often involves difficulty with borderline cases that could fairly be assigned either of the two binary class memberships. In such situations the indicated class membership is often highly subjective and subject to, for instance, a measurement error. In other situations the intermediate level of a three-level ordinal factor may sometimes be explicitly reserved for cases which could likely belong to either of the two binary classes.
Optimizing the Analysis of Stroke Trials (OAST) Collaboration(3)	2007	Acute stroke	Data from 55 datasets (47 trials, 54,173 patients) from acute, rehabilitation and stroke unit trials studying the effects of interventions were used to asses which statistical approaches are most efficient in analyzing outcomes from stroke trials. The test results differed substantially so that approaches which use the ordered nature of functional outcome data (ordinal logistic regression, t test, robust ranks test, bootstrapping the difference in mean rank) were more efficient statistically than those which collapse the data into 2 groups (chi(2); ANOVA, $P<0.001$). The findings were consistent across different types and sizes of trial and for the different measures of functional outcome.
Saver(13)	2007	Acute stroke	Dichotomized, global statistic, responder, and shift analyses each offer distinctive benefits and drawbacks. Choice of primary end point analytic technique should be tailored to the study population, expected treatment response, and study purpose. Shift analysis generally provides the most comprehensive index of a treatment's clinical impact. Shift analysis gauges change in outcome distributions over the full range of ascertained outcomes, incorporating benefit and harm at all health state transitions valued by patients and clinicians, and often increasing study power.
Senn(33)	2009	-	Biostatisticians have frequently uncritically accepted the measurements provided by their medical colleagues engaged in clinical research, which often involve considerable loss of information. Particularly, unfortunate is the widespread use of the so-called 'responder analysis', which may involve not only a loss of information through dichotomization, but also extravagant and unjustified causal inference regarding individual treatment effects at the patient level, and, increasingly, the use of the so-called number needed to treat scale of measurement. Other problems involve inefficient use of baseline measurements, the use of covariates measured after the start of treatment, the interpretation of titrations and composite response measures. Statisticians should pay more attention to this aspect of their work.

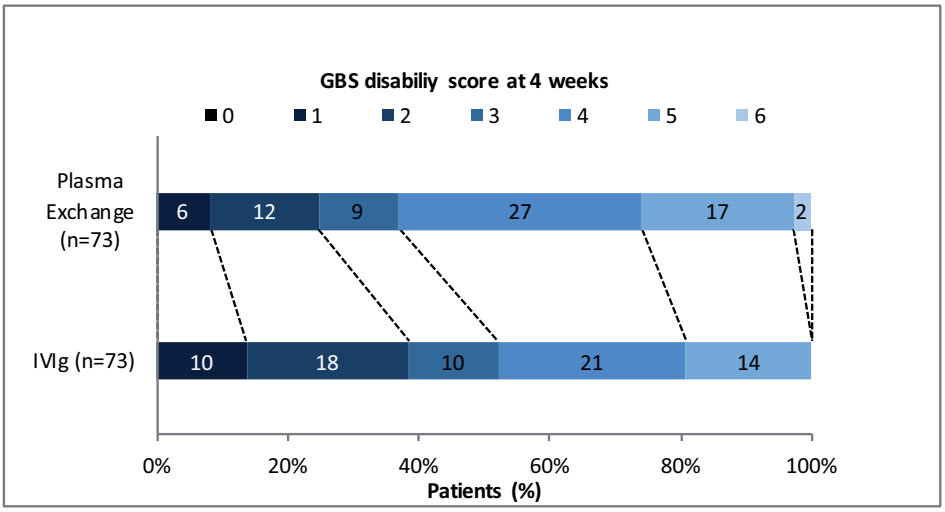
Table S1. Overview of a selection of methodological studies considering covariate adjustment and ordinal analysis in RCTs. (continued)

First author	Year	Field	Key findings and conclusions
McHugh(11)	2010	Traumatic brain injury	This study was based on simulations, which were built around a database of patient-level data extracted from eight Phase III trials and three observational studies in traumatic brain injury. Two different putative treatment effects were explored, one which followed the proportional odds model, and the other which assumed that the effect of the intervention was to reduce the risk of death without changing the distribution of outcomes within survivors. The simulation results show substantial efficiency gains. Use of the sliding dichotomy allows sample sizes to be reduced by up to 40% without loss of statistical power. The proportional odds model gives modest additional gains over and above the gains achieved by use of the sliding dichotomy.
Roozenbeek(12)	2011	Traumatic brain injury	Two techniques for ordinal analysis were applied using data from the CRASH trial (n = 9,554): proportional odds analysis and the sliding dichotomy approach, where the GOS is dichotomized at different cut-offs according to baseline prognostic risk. These approaches were compared to dichotomous analysis. Ordinal analysis with proportional odds regression or sliding dichotomy showed highly statistically significant treatment effects, with 2.05-fold and 2.56-fold higher information density compared to the dichotomous approach respectively. Analysis of the CRASH trial data confirmed that ordinal analysis of outcome substantially increases statistical power.
Diaz(34)	2016	Acute stroke	A general method for estimating the effect of a treatment on an ordinal outcome in randomized trials is presented. The method is robust in that it does not rely on the proportional odds assumption. Our estimator leverages information in prognostic baseline variables, and has all of the following properties: (i) it is consistent; (ii) it is locally efficient; (iii) it is guaranteed to have equal or b;etter asymptotic precision than both the inverse probability-weighted and the unadjusted estimators. The estimator is demonstrated in simulations based on resampling from a completed randomized clinical trial of a new treatment for stroke; we show potential gains of up to 39% in relative efficiency compared to the unadjusted estimator.

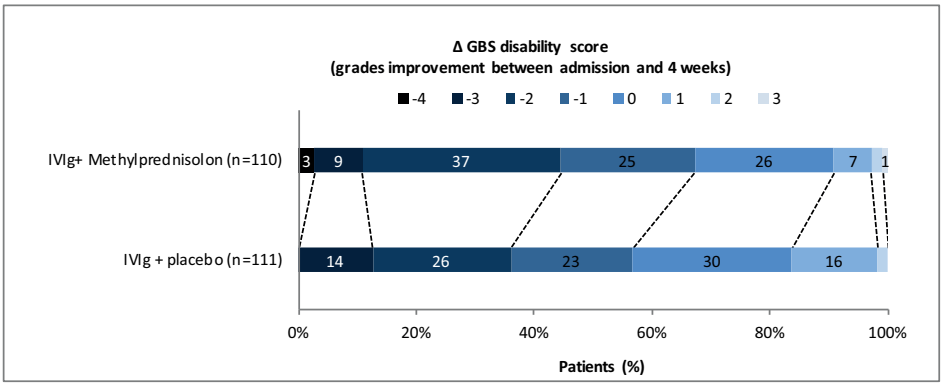
a)


GBS disablity score at 4 weeks
0
1
2
3
4
5
6
IVIg+ Methylprednisolon (n=110)
5
13
43
12
23
12
2
IVIg + placebo (n=111)
24
31
10
31
14
1
0%
20%
40%
60%
80%
100%
Patients (%)

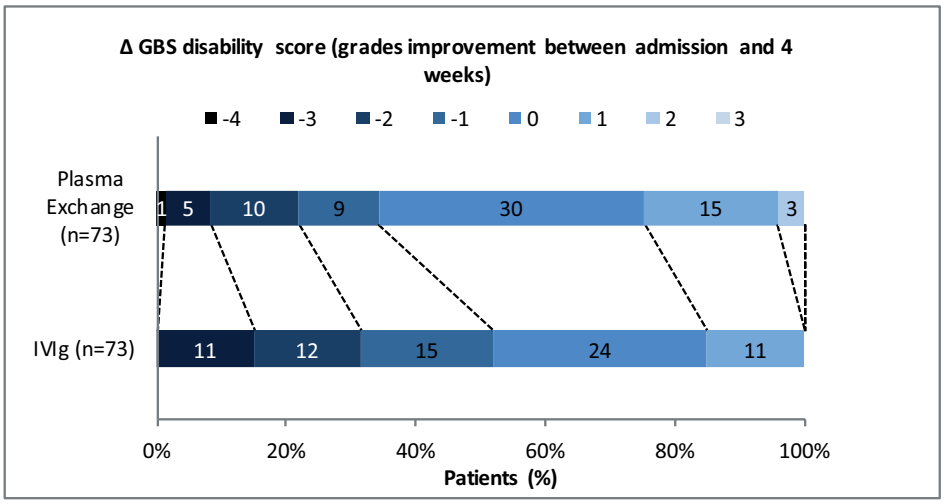
b)


GBS disabiliy score at 4 weeks
0
1
2
3
4
5
6
Plasma Exchange (n=73)
6
12
9
27
17
2
IVIg (n=73)
10
18
10
21
14
0%
20%
40%
60%
80%
100%
Patients (%)

c)


Δ GBS disability score
(grades improvement between admission and 4 weeks)
-4
-3
-2
-1
0
1
2
3
IVIg+ Methylprednisolon (n=110)
3
9
37
25
26
7
1
IVIg + placebo (n=111)
14
26
23
30
16
0%
20%
40%
60%
80%
100%
Patients (%)

d)



Appendix 1. Distribution of the GBS disability score at four weeks and improvement on the GBS disability score after four weeks in the IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (a and c) and PE vs IVIg trial (b and d).