Quality of Reporting Randomized Controlled Trials in Five Leading Neurology Journals in 2008 and 2013 Using the Modified "Risk of Bias" Tool

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BACKGROUND: **To examine the risk of bias of methodological quality of reporting randomized clinical trials (RCTs) in major neurology journals before and after the update (2011) of Cochrane risk of bias tool.**

METHODS: **RCTs in 5 leading neurology journals in 2008 and 2013 were searched systematically. Characteristics were extracted based on the list of the modified Cochrane Collaboration's tool. Country, number of patients, type of intervention, and funding source also were examined for further analysis.**

RESULTS: **A total of 138 RCTs were enrolled in this study. The rates of following a trial plan were 61.6% for the allocation generation, 52.9% for the allocation concealment, 84.8% for the blinding of the participants or the personnel, 34.8% for the blinding of outcome assessment, 78.3% for the incomplete outcome data, and 67.4% for the selective reporting. A significant setback was found in "the selective reporting" in 2013 than that in 2008. Trials performed by multi-centers and on a large scale had significantly more "low risk of bias" trials. Not only the number of surgical trials (5.8%) was much less than that of trials using drugs (73.9%), but also the reporting quality of surgical trials were worse ($P = 0.008$). Finally, only 17.4% trials met the criterion of "low risk of bias."**

CONCLUSIONS: **The modified "risk of bias" tool is an improved version for assessment. Methodological quality of reporting RCTs in the 5neurology journals is unsatisfactory, especially that for surgical RCTs, and it could be further improved.**

INTRODUCTION

Disorders of the nervous system have been recognized as important causes of death and disability around the world, with 1 in every 9 individuals dying from such a disorder.[1] For their prevention and management, randomized controlled trials (RCTs) have been used extensively and have an important role in screening effective agents and approaches.[2] According to the U.S. Preventive Services Task Force,[3] the top level (level I) evidence of evidence-based medicine should be obtained from at least one properly designed RCT. Therefore, the methodologic quality of the RCTs may influence the conclusions of the evidence-based studies and then finally affect clinical decisions.[4,5]

It has been estimated that the poor quality of reporting of key methodologic features in RCTs might lead to the misrepresentation of inferior or even harmful treatments.[6] It was estimated that intervention effects were more exaggerated in small-scale trials than in large-scale trials, with inadequate allocation sequence generation (ratio of odds ratios, 0.46; 95% confidence interval [CI] 0.25–0.83; P = 0.011), inadequate allocation concealment (ratio of odds ratios, 0.49; 95% CI 0.27–0.86; P = 0.014), and no double blinding (ratio of odds ratios, 0.52; 95% CI 0.28–0.96; P = 0.01).[7] In addition, when meta-reviews and guidelines include RCTs of low quality without careful assessment, conclusions will be compromised greatly. Therefore, a regular evaluation of RCTs is essential.

Key words
- Cochrane Collaboration's tool
- Methodological quality
- Neurology
- Randomized controlled trials
- Risk of bias

Abbreviations and Acronyms
CI: Confidence interval
RCT: Randomized clinical trial

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In 2008, a new tool, called the "risk of bias" list, was published by the Cochrane[8] to assess the quality of RCTs. In 2011, a revision was produced after a 3-stage project of evaluation of the implementation.[9] The "risk of bias" list now contains a 7-item checklist, focusing on reporting of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. In addition, some of the domains listed in the Cochrane Collaboration's Tool also need improvement, because currently most multicenter RCTs use real-time central randomization. Therefore, we first modified the details of the tool in this study.

The reported methodology of RCTs has been assessed and published on various fields previously, including complementary and traditional medicine,[10] surgery,[4,11,12] gastroenterology,[13] and anesthesiology.[14] Little is known, however, about the methodologic quality of reporting RCTs on neurology and before and after the update of the "risk of bias" list in 2011. As a result, we systematically appraised the quality of reporting RCTs in 2008 and 2013 in 5 prominent neurology journals.

METHODS

To appraise the current 5-year reporting methodologic quality of RCTs on neurology, we decided to investigate the top 5 journals that performed with the highest impact factor as following: *Annals of Neurology*, *Archives of Neurology* (now *JAMA Neurology*), *Lancet Neurology*, *Neurology*, and *Journal of Neuroscience*. Their reported methodology has never been studied systematically. To identify the effects of the "risk of bias" list updated in 2011 and eliminate its impact on similar years, we included articles published in 2008 and 2013.

The methods used in this article were referred to those described previously.[4,13,15] To summarize, trials were thought to be RCTs if the words "randomization," "random," or "randomly" were found in the text to describe the allocation method. Furthermore, trials published as abstracts, quasi-randomized trials, as part of some large RCTs, trials with animals or subgroups analysis of RCTs, and observational studies nested within RCTs were excluded from the study. Ethics approval is not applicable, because this manuscript does not report on or involve the use of any animal or human data or tissue.

The 2 co-first authors hand-searched all the RCTs of the 5 journals published in 2008 and 2013 in the PubMed database from the 5 journals to include all potentially eligible trials. Relevant trials were then identified and analyzed.

Publishing, geographical, epidemiologic, and clinical characteristics were extracted. Positive outcome was defined adequate if primary favorable outcome was stated explicitly by statistical significance. For the conflict of interests, "not specific" was defined if the information was not found in the article, and "none" was defined if the authors declared that no funds supported the study.

The following list was formed after a minor modification of the Cochrane Collaboration's tool for assessing risk of bias on RCTs,[9] and then all studies were assessed with judgments of "low," "high," or "unclear" risk of bias. These items are defined as follows:

1. Generation of allocation (selection bias): low risk if the allocation follows a trial plan (e.g., randomization: computer-generated sequence, random table, coin toss; or a minimization method; or permuted block randomization).[16]
2. Concealment of allocation (selection bias): low risk if a proper method follows a trial plan to avoid knowing or expecting the allocation sequence in advance (e.g., envelopes, central/pharmacy randomization or independent person). In real-time randomization, it is regarded as low risk if the treatment assignment is made at the time of subject randomization and the risk of allocation concealment failure is eliminated.
3. Blinding of participants and personnel (performance bias): low risk if the procedure follows a trial plan that states any type of blinding of participants and researchers.
4. Blinding of outcome assessment (detection bias): low risk if the assessment follows a trial plan that the person who did the outcome assessment was unaware of the allocation.
5. Incomplete outcome data (attrition bias): low risk if the completeness of outcome data for each main outcome, including attrition and exclusion from the analysis, follows a trial plan. Low risk if authors performed an intention-to-treat analysis or used imputation to account for missing data.
6. Selective reporting (reporting bias): low risk if the study is in accordance with the study protocol. Protocols were searched by trial numbers published in the article. Unclear risk of bias was defined if the protocol was not found.

"Low risk of bias" trial was defined as low risk of bias for all key domains within a trial, "unclear risk of bias" trial features low or unclear risk of bias for all key domains, and "high risk of bias" trial has high risk of bias for one or more key domains.[9] We defined it as "summarized risk of bias" in this study.

The agreement of the 2 authors (Q.C.M. and WP.L.) was rated by calculation of the kappa value. Any disagreement was settled by discussion between the 2 reviewers. The senior reviewer (X.Z.) then sought to make a decision if the discrepancies could not be solved by consensus.

Descriptive statistics (mean, standard deviation) were used. All statistical analyses were implemented with SAS 9.1 software (SAS Institute, Cary, North Carolina, USA). For the comparison of proportions of attributes, the χ^2 test was used; for the comparison of the risk levels between the 2 years and among the journals, the Cochran-Mantel-Haenszel test was performed; and for the comparison among the type of interventions, since the expected frequency is less than 5, the Fisher exact test was used. A $P < 0.05$ was considered a statistically significant difference.

RESULTS

A total of 222 studies were retrieved from the 5 journals. Of these 222 studies, 84 were excluded because they had a non-randomized design or were subgroup analyses, letters, or reviews, a pooled analysis of RCTs, or cost-effective studies alongside RCTs (**Figure 1**). As a result, 138 trials were suitable for the analysis, including 12 from *Annals of Neurology*, 14 from *Archives of Neurology* (now *JAMA Neurology*), 42 from *Lancet Neurology*, 56 from *Neurology* and 14 from *Journal of Neuroscience*. A total of 75 trials were published in 2008 and 63 trials in 2013. The details of these data are listed in the **Supplementary Tables 1**, **2**, and **3**.

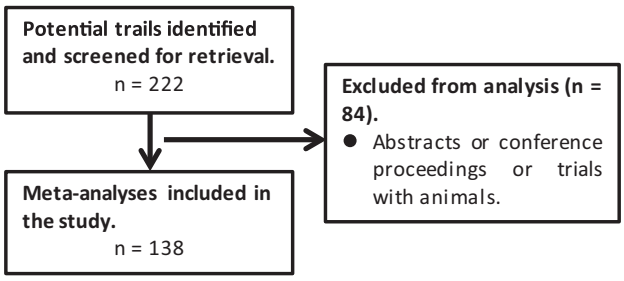

Figure 1. Flow diagram of the randomized controlled trials included.

Major characteristics of the included trials are shown in Table 1. Generally, the 138 trials included a median of 117.5 patients (25th percentile 35.25, 75th percentile 400.25). More than one half of all the trials were reported from the United States (63.0%), and Europe contributed 29.7%. Two-thirds of all trials were multicenter (69.6%). Public foundations supported 50.7% trials. Medical intervention was the most used treatment (73.9%). For outcomes, more positive results (69.6%) than negative results (24.6%) were reported in the trials.

Kappa values for the interobserver agreement between the 2 reviewers were calculated and all these values indicated almost perfect or substantial agreement: 0.87 for the generation of the allocation sequence, 0.91 for the allocation concealment, 0.76 for blinding of the participants and personnel, 0.89 for the blinding of outcome assessment, 0.71 for the incomplete outcome data, 0.74 for the selective reporting, and 0.97 for the summarized risk of bias.

For the methodologic quality of reporting RCTs and among the 138 trials, 61.6% trials followed a trial plan for the allocation generation, 52.9% followed a trial plan for the allocation concealment, 84.8% performed the blinding of the participants or personnel, only 34.8% performed the blinding of outcome assessment, 78.3% had low risk of bias for the incomplete outcome data, 67.4% were adequate for the selective reporting, and finally 17.4% met the criteria of "low risk of bias" trials. Compared with trials in 2008, there was a significant decrease in 2013 in the selective reporting ($P = 0.002$) (Figure 2).

Among the 5 journals, *Lancet Neurology* had the most trials that followed a trial plan for the allocation generation ($P < 0.001$, $P < 0.001$ vs. *Annals of Neurology* and *Journal of Neuroscience*, $P = 0.010$ vs. *JAMA Neurology* and $P = 0.017$ vs. *Neurology*). In contrast, *Journal of Neuroscience* performed the worst for concealment of allocation ($P < 0.001$, $P = 0.026$ *vs.* *Annals of Neurology* and $P < 0.001$ vs. *Lancet Neurology* and *Neurology*), selective reporting ($P < 0.001$, $P = 0.037$ vs. *JAMA Neurology* and $P < 0.001$ vs. *Lancet Neurology*, *Annals of Neurology* and *Neurology*), and incomplete outcome data ($P < 0.001$, $P = 0.037$ vs. *JAMA Neurology* and $P < 0.001$ vs. *Lancet Neurology*, *Annals of Neurology*, and *Neurology*). There was no significant difference, however, for numbers of "low risk of bias" trials among the 5 journals ($P = 0.064$) (Figure 3).

According to different strata, it was found generally for the number of "low risk of bias" trials that there were significant differences between single-center/multicenter ($P = 0.009$) and small-scale/large-scale trials ($N > 100/N \leq 100$) ($P = 0.004$), and among type of interventions ($P = 0.009$, $P = 0.008$ surgery vs. medicine) (Table 2).

DISCUSSION

In the current study, we first modified the list and then described the methodologic quality of reporting RCTs in 5 major neurology journals in 2008 and 2013. Two-thirds of all the trials were reported from the United States, two-thirds of all trials were multicenter, and half of trials were supported by a public foundation. It was noted that most of RCTs were at low risk of bias or unclear risk of bias for the 6 methodologic quality domains; however, only 17.4% finally were defined as "low risk of bias" trials. A significant backslide was found for the selective reporting in 2013 than 2008. *Lancet Neurology* had the most trials that followed a trial plan for generation of allocation. It was significant that the number of "low risk of bias" trials performed at the multicenter or at a large scale was more for "low risk of bias" trials. As a result, these findings suggest that more efforts can be made to improve the quality of the reported methodology for RCTs in major neurology journals.

It generally is believed that the Cochrane Collaboration tool is important for authors of RCTs to follow to improve their reporting and transparency. Although the tool is not a perfect quality assessment instrument, we also can find and analyze mutual defects of RCTs by using this tool. And, in this study, we did a minor revision from the updated list to adapt the progression of the RCTs.

To reduce selection bias, randomization-based inference is a fundamental principle in experimental design and in survey sampling. According to Lachin et al.,[17] an ideal randomization procedure would set the goals for achieving maximization of statistical power, minimization of selection bias, and minimization of allocation bias. In addition, the minimization methods,[18] a nonrandomization procedure proposed by Taves and Pocock and Simon, and the permuted block randomization[16] often were used as for controlling marginal imbalances for baseline covariates. Neither minimization nor permuted blocks randomization, however, are valid randomization methods. Conducted improperly, they might lead to a high risk of bias, specifically selection bias, because they preclude the possibility of allocation concealment. Moreover, the Cochrane "risk of bias" tool itself is flawed for equating minimization with true randomization.

In this study, we proposed that a trial considered with low risk of bias in allocation generation should clearly report the exact methods so that readers can assess the risk of bias accordingly, and we also creatively added the nonrandomization procedure as a criterion onto the list. A total of 38.4% RCTs did not report adequate methods (except for 1 RCT using a minimization method), signifying possibly a high risk of bias for the allocation process.

Allocation concealment is another way to reduce selective bias. It is used to keep the person who is enrolling the next participant in the study unaware of the treatment assignment. No one knows exactly what the next treatment assignment will be until the actual randomization takes place. It is therefore

Table 1. Principal Characteristics of the Included Trials

	All Trials (%)	2008 (%)	2013 (%)	*P* Value	*Annals of Neurology* (%)	*JAMA Neurology* (%)	*Lancet Neurology* (%)	*Neurology* (%)	*Journal of Neuroscience* (%)	*P* Value
Number	138 (100.0)	75 (54.3)	63 (45.7)		12 (8.7)	14 (10.1)	42 (30.4)	56 (40.6)	14 (10.1)	
Region/country										
U.S.	87 (63.0)	46 (61.3)	41 (65.1)		9 (75.0)	11 (78.6)	13 (31.0)	34 (60.7)	4 (28.6)	
Europe	41 (29.7)	25 (33.3)	16 (25.4)		3 (25.0)	3 (21.4)	26 (61.9)	19 (33.9)	7 (50.0)	
Asia/Oceania	6 (4.3)	3 (4.0)	3 (4.8)	0.677	0 (0.0)	0 (0.0)	3 (7.1)	2 (3.6)	1 (7.1)	0.002*
Africa/South America	1 (0.7)	0 (0.0)	1 (1.6)		0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Canada	3 (2.2)	1 (1.3)	2 (3.2)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	
Center										
Single center	42 (30.4)	15 (20.0)	27 (42.9)	0.004*	4 (33.3)	7 (50.0)	0 (0.0)	18 (32.1)	13 (92.9)	<0.001*
Multicenter	96 (69.6)	60 (80.0)	36 (57.1)		8 (66.7)	7 (50.0)	42 (100.0)	38 (67.9)	1 (7.1)	
Conflicts of interest										
Industry	48 (34.8)	34 (45.3)	14 (22.2)		4 (33.3)	2 (14.3)	16 (38.1)	26 (46.4)	0 (0.0)	
Public	70 (50.7)	31 (41.3)	39 (61.9)		3 (25.0)	8 (57.1)	22 (52.4)	24 (42.9)	13 (92.9)	
Both	16 (11.6)	8 (10.7)	8 (12.7)	0.016*	5 (41.7)	3 (21.4)	4 (9.5)	3 (5.4)	1 (7.1)	0.003*
Not specific	2 (1.4)	2 (2.7)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	
None	2 (1.4)	0 (0.0)	2 (3.2)		0 (0.0)	1 (7.1)	0 (0.0)	1 (1.8)	0 (0.0)	
Type of intervention										
Medicine	102 (73.9)	58 (77.3)	44 (69.8)	0.436	11 (91.7)	9 (64.3)	28 (66.7)	41 (73.2)	13 (92.9)	0.204
Surgery	8 (5.8)	4 (5.3)	4 (6.3)		0 (0.0)	0 (0.0)	6 (14.3)	2 (3.6)	0 (0.0)	
Rehabilitation	5 (3.6)	1 (1.3)	4 (6.3)		1 (8.3)	1 (7.1)	1 (2.4)	2 (3.6)	0 (0.0)	
Others	23 (16.7)	12 (16.0)	11 (17.5)		0 (0.0)	4 (28.6)	7 (16.7)	11 (19.6)	1 (7.1)	
Outcome										
Positive outcome	96 (69.6)	49 (65.3)	47 (74.6)		10 (83.3)	10 (71.4)	25 (59.5)	39 (69.6)	12 (85.7)	
Negative outcome	34 (24.6)	21 (28.0)	13 (20.6)	0.501	0 (0.0)	3 (21.4)	14 (33.3)	17 (30.4)	0 (0.0)	<0.001*
No difference	8 (5.8)	5 (6.7)	3 (4.8)		2 (16.7)	1 (7.1)	3 (7.1)	0 (0.0)	2 (14.3)	

*$P < 0.05$.

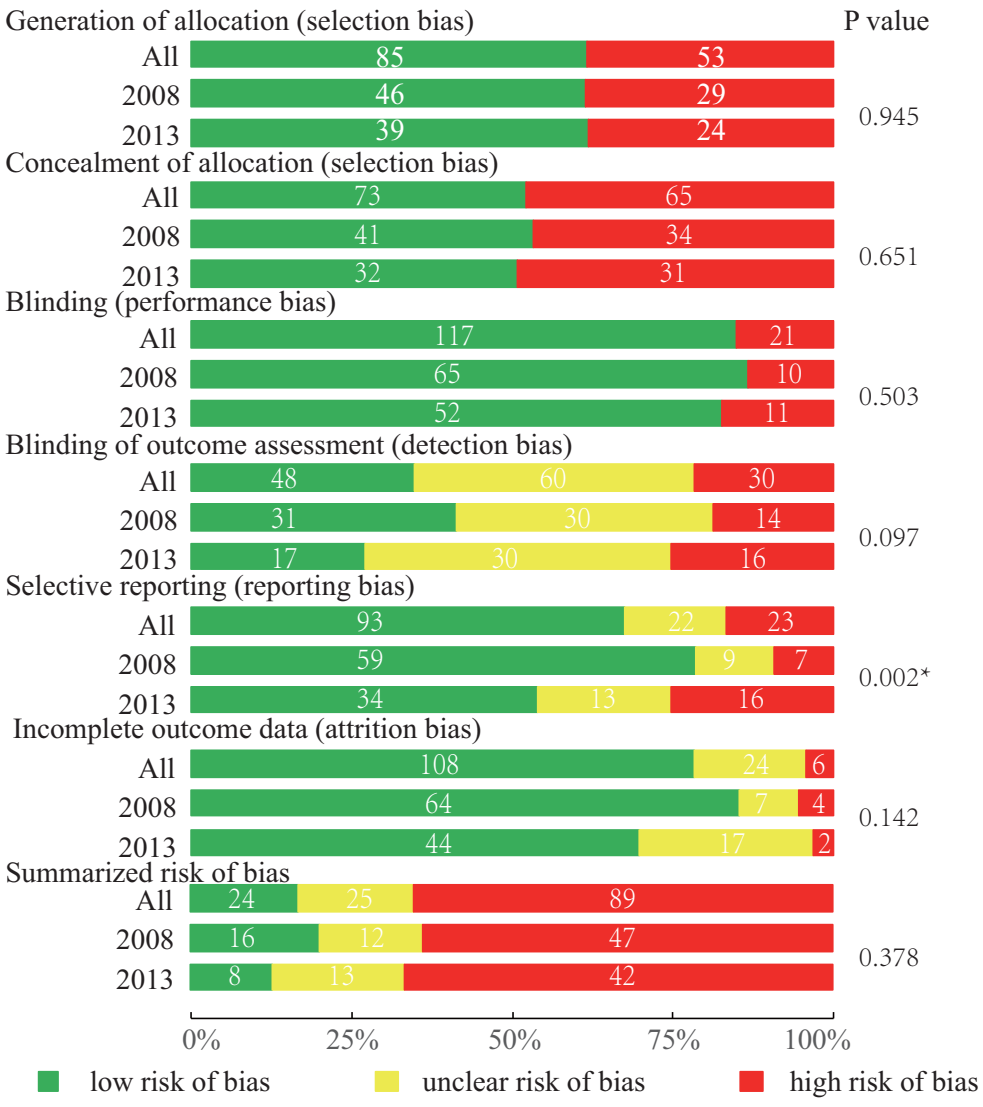

Figure 2. Risk of bias assessment summary for included randomized controlled trials using the Cochrane Collaboration's risk of bias tool in 2008 and 2013. $P < 0.05$.

recommended that the allocation concealment methods should be reported in detail not only in an RCT's protocol but also in the publication of its results.[19] Standard methods include central/pharmacy-controlled randomization, sealed envelopes, and an independent unit.[20] We also modified the list by inserting the real-time randomization. It is believed to eliminate the risk of allocation concealment failure because the treatment assignment is made at the time of subject randomization. Our study found that 47.1% of trials in this study had high risk of bias for allocation concealment. Wood et al.[21] conducted a meta-epidemiologic study and concluded that the results of RCTs with inadequate or unclear allocation concealment seemed to be biased. As a result, editors and authors should pay more attention to allocation concealment.

To avoid performance bias and detection bias, blinding of participants and personnel and blinding of outcome assessment are necessary. In the first (2008) version of the Cochrane Collaboration's tool, there was only a single assessment for blinding, but it was revised into 2 assessments because they belonged to different domains of bias and blinding should be assessed across all the outcome.[9] In the practice of neurology, some outcomes were highly subjective, and the patients' knowledge of the intervention received may influence the outcomes, so the blinding of patients is critical. In general, it is difficult to conduct blinding in many nondrug trials, but blinding of outcome assessment is much easier and more attention should be paid to it.

To minimize attrition bias, attrition and exclusion from the analysis should be described adequately. Missing data caused by

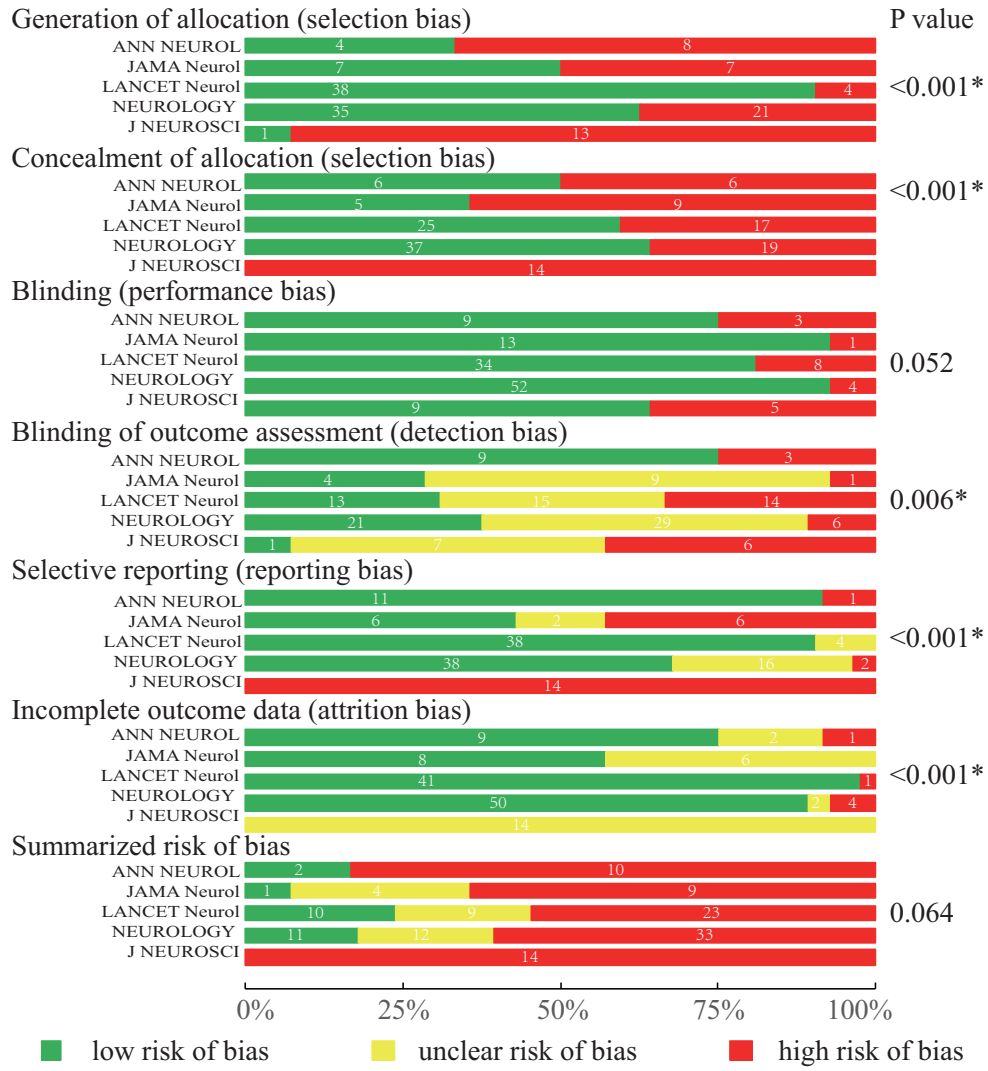

Figure 3. Risk of bias assessment summary for included randomized controlled trials using the Cochrane Collaboration's risk of bias tool in 5 journals. $P < 0.05$.

patients dropping out of the study before completion is a major problem in the analysis of clinical trials. It can result in biased treatment comparison and influence the overall statistical power of the study.[22,23] In the CONSORT (Consolidated Standards of Reporting Trials) statement,[24] a drop-out exceeding 20% was regarded inadequate for handling of dropouts; however, in this new tool,[9] 20% was not adopted because there is no guarantee that results from a study with a drop-out rate lower than 20% or 21% are at low risk of bias. In addition, de Bruin et al.[25] revealed that attrition could be nonrandom, so it is important to report and analyze the details of attrition and exclusion as well, including adverse events, lack of efficacy, lost to follow-up, death, and so on.

For the reduction of reporting bias, selective outcome reporting should be reduced by providing a study protocol. We can compare outcomes both in the protocol and published report if the protocol is available. In the future, a mandatory registration of trials should become more common, with a detailed description of the study available in a trial registry. In addition, authors who perform a review should assess the section of methods in published articles carefully. In this study, 67.4% trials were satisfied and had low risk of bias for selective reporting, which still might be improved.

The "low risk of bias" trials were defined as having a low risk of bias for all key domains within a trial. Only 24 trials (17.4%) met these criteria. Trials that were large scale (N > 100) (P = 0.004) and conducted in multiple enters (P = 0.009) showed more low risk of bias, which indicates that multicenters trials with adequate numbers of participants might improve the methodologic quality of RCTs published in neurology journals. Interestingly, the number of surgical trials (5.8%) was much lower than that of trials that used medicine (73.9%), and surgical trials also turned out to

Table 2. Methodologic Quality of Reporting RCTs in the 5 Journals in 2008 and 2013 According to Different Strata

	"Low Risk of Bias" Trials	"High Risk of Bias" Trials	"Unclear Risk of Bias" Trials	*P* Value
Region/country				
U.S.	13 (14.9)	59 (67.8)	15 (17.2)	0.080
Europe	9 (17.1)	36 (58.5)	13 (24.4)	
Asia/Oceania	4 (66.7)	2 (33.3)	0 (0.0)	
Africa/South America	0 (0.0)	1 (100.0)	0 (0.0)	
Others	0 (0.0)	3 (100.0)	0 (0.0)	
Center				
Single center	4 (9.5)	35 (83.3)	3 (7.1)	0.009*
Multicenter	20 (20.8)	54 (56.3)	22 (22.9)	
Funding				
Industry	7 (14.6)	27 (56.3)	14 (29.2)	0.283
Public	15 (21.4)	47 (67.1)	8 (11.4)	
Both	2 (12.5)	12 (75.0)	2 (12.5)	
Not specific	0 (0.0)	2 (100.0)	0 (0.0)	
None	0 (0.0)	1 (50.0)	1 (50.0)	
Type of interventions				
Medicine	18 (17.6)	62 (60.8)	22 (21.6)	<0.001*
Surgery	1 (12.5)	2 (25.0)	5 (62.5)	
Rehabilitation	0 (0.0)	4 (80.0)	1 (20.0)	
Others	5 (21.7)	18 (78.3)	0 (0.0)	
No. patients				
>100	17 (22.4)	42 (55.3)	17 (22.4)	0.004*
≤100	7 (11.3)	47 (75.8)	8 (12.9)	

*$P < 0.05$.

be worse in the reporting quality ($P = 0.008$). Because surgical intervention in neurology diseases is very important, more RCTs should be encouraged to be performed, and their quality also should be examined systematically.

In other medical disciplines, the methodologic quality of RCTs was assessed tools similar to Cochrane Collaboration's. Sinha et al.[26] reported methodologic quality of RCTs of pharmacologic interventions in children and adults. Many trials had an unclear risk of bias for allocation concealment (65% adult, 52% pediatric). A total of 59% pediatric trials and 41% adult trials had a low risk of bias for random sequence generation and 63% pediatric trials and 48% adult trials had a low risk of bias for blinding of outcome assessment. Kim et al.[10] found a low proportion of trials reported participant blinding (34.2%) and outcome assessor blinding (22.5%) on complementary and traditional medicine in the Korean literature. Comparatively speaking, the quality of RCTs in neurology journals seems more satisfying.

The current study had several limitations. First, the quality of methodological details we focused on might differ from the quality of actual study.[27] It means that a well-designed and well-conducted trial may be considered with high risk of bias if the methodologic methods were reported inadequately. Second, we chose trials in 2008 and 2013 to compare the reporting quality before and after the publication of the tool; however, this study did not show the trend in these 5 years. Third, although 5 highest impact factor neurology journals were considered, a number of neurology-related RCTs are published in other non-neurology or lower-impact journals. To some extent, this study reflected the quality of reporting RCTs in a better level of neurology trials. Finally, although the reporting of a trial was regarded at low risk of bias according to the Cochrane Collaboration tool in this study, we should still bear in mind whether the trial met the scientific criteria and chose the appropriate procedure.

CONCLUSIONS

We modified the "risk of bias" tool and provided an improved version for RCTs performed nowadays. The current study showed that the quality of the methods of RCTs in 5 major neurology

journals was unsatisfactory and could be further improved; in particular, the number of high reporting quality surgical RCTs was far from satisfactory. More effort should be devoted by journal editors, authors, and readers to improve the methodology of randomized trials for to achieve credible clinical evidence.

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SUPPLEMENTARY DATA

Supplementary Table 1. Methodologic Reporting Quality of RCTs in 2008 and 2013

Methodological Quality Characteristic	All Trials (%)	2008 (%)	2013 (%)	*P* Value
Generation of allocation				
Low risk of bias	85 (61.6)	46 (61.3)	39 (61.9)	0.945
High risk of bias	53 (38.4)	29 (38.7)	24 (38.1)	
Concealment of allocation				
Low risk of bias	73 (52.9)	41 (54.7)	32 (50.8)	0.651
High risk of bias	65 (47.1)	34 (45.3)	31 (49.2)	
Blinding: any type of blinding				
Low risk of bias	117 (84.8)	65 (86.7)	52 (82.5)	0.503
High risk of bias	21 (15.2)	10 (13.3)	11 (17.5)	
Blinding of outcome assessment				
Low risk of bias	48 (34.8)	31 (41.3)	17 (27.0)	0.097
High risk of bias	30 (21.7)	14 (18.7)	16 (25.4)	
Unclear risk of bias	60 (43.5)	30 (40.0)	30 (47.6)	
Selective reporting				
Low risk of bias	93 (67.4)	59 (78.7)	34 (54.0)	0.002*
High risk of bias	23 (16.7)	7 (9.3)	16 (25.4)	
Unclear risk of bias	22 (15.9)	9 (12.0)	13 (20.6)	
Incomplete outcome data				
Low risk of bias	108 (78.3)	64 (85.3)	44 (69.8)	0.142
High risk of bias	6 (4.3)	4 (5.3)	2 (3.2)	
Unclear risk of bias	24 (17.4)	7 (9.3)	17 (27.0)	
Trials				
"Low risk of bias" trials	24 (17.4)	16 (20.0)	8 (12.7)	0.378
"Unclear risk of bias" trials	25 (17.4)	12 (16.0)	13 (20.6)	
"High risk of bias" trials	89 (65.2)	47 (64.0)	42 (66.7)	

RCT, randomized controlled trial.
*$P < 0.05$.

Supplementary Table 2. Methodologic Reporting Quality of RCTs in 5 Journals

Methodological Quality Characteristic	*Annals of Neurology*	*JAMA Neurology*	*Lancet Neurology*	*Neurology*	*Journal of Neuroscience*	*P* Value
Generation of allocation						
Low risk of bias	4 (33.3)	7 (50.0)	38 (90.5)	35 (62.5)	1 (7.1)	<0.001*
High risk of bias	8 (66.7)	7 (50.0)	4 (9.5)	21 (37.5)	13 (92.9)	
Concealment of allocation:						
Low risk of bias	6 (50.0)	5 (35.7)	25 (59.5)	37 (66.1)	0 (0.0)	<0.001*
High risk of bias	6 (50.0)	9 (64.3)	17 (40.5)	19 (33.9)	14 (100.0)	
Blinding: any type of blinding						
Low risk of bias	9 (75.0)	13 (92.9)	34 (81.0)	52 (92.9)	9 (64.3)	0.052
High risk of bias	3 (25.0)	1 (7.1)	8 (19.0)	4 (7.1)	5 (35.7)	
Blinding of outcome assessment						
Low risk of bias	9 (75.0)	4 (28.6)	13 (31.0)	21 (37.5)	1 (7.1)	
High risk of bias	3 (25.0)	1 (7.1)	14 (33.3)	6 (10.7)	6 (42.9)	0.006*
Unclear risk of bias	0 (0.0)	9 (64.3)	15 (35.7)	29 (51.8)	7 (50.0)	
Selective reporting						
Low risk of bias	11 (91.7)	6 (42.9)	38 (90.5)	38 (67.9)	0 (0.0)	
High risk of bias	1 (8.3)	6 (42.9)	0 (0.0)	2 (3.6)	14 (100.0)	<0.001*
Unclear risk of bias	0 (0.0)	2 (14.3)	4 (9.5)	16 (28.6)	0 (0.0)	
Incomplete outcome data						
Low risk of bias	9 (75.0)	8 (57.1)	41 (97.6)	50 (89.3)	0 (0.0)	
High risk of bias	1 (8.3)	0 (0.0)	1 (2.4)	4 (7.1)	0 (0.0)	<0.001*
Unclear risk of bias	2 (16.7)	6 (42.9)	0 (0.0)	2 (3.6)	14 (100.0)	
Trials						
"Low risk of bias" trials	2 (16.7)	1 (7.1)	10 (23.8)	11 (19.6)	0 (0.0)	
"High risk of bias" trials	10 (83.3)	9 (64.3)	23 (54.8)	33 (68.9)	14 (100.0)	0.064
"Unclear risk of bias" trials	0 (0.0)	4 (28.6)	9 (21.4)	12 (21.4)	0 (0.0)	

*$P < 0.05$.

Supplementary Table 3. Details of All Studies

No.	Author/ Year	Journal	Single/ Multicenter	Country	Conflicts of Interest Statements	Type of Interventions	No. of Patients	Primary Outcome Explicitly Stated	Sample Size Calculation	Baseline Present	Generation of Allocation	Concealment of Allocation	Blinding: Any Type of Blinding	Blinding of Outcome Assessment	Selective Reporting	Incomplete Outcome Data
1	Garren H, 2008	*Ann Neurol*	Multi	U.S.	Industry	Medicine	289	Positive	0	1	0	Central/pharmacy	1	1	PPA	1
2	Kadir A, 2008	*Ann Neurol*	Single	Sweden	Both	Medicine	20	Positive	0	1	0	0	1	1	0	?
3	LeWitt PA, 2008	*Ann Neurol*	Multi	U.S.	Industry	Medicine	196	Positive	1	1	0	0	1	1	ITT	1
4	Morrell, MJ, 2008	*Ann Neurol*	Multi	U.S.	Industry	Medicine	447	Positive	0	1	0	0	0	1	ITT	1
5	Ranoux D, 2008	*Ann Neurol*	Single	France	Public	Medicine	29	Positive	0	1	Random table	Central/pharmacy	1	1	ITT	1
6	Schiffmann R, 2008	*Ann Neurol*	Multi	U.S.	Both	Medicine	30	Positive	0	1	0	0	0	1	ITT	0
7	Wagner KR, 2008	*Ann Neurol*	Multi	U.S.	Both	Medicine	116	No difference	0	1	Computer	Others	1	0	ITT	1
8	Bermel RA, 2013	*Ann Neurol*	Multi	U.S.	Industry	Medicine	136	Positive	0	1	0	0	0	0	PPA	1
9	Lublin FD, 2013	*Ann Neurol*	Multi	U.S.	Public	Medicine	1008	No difference	1	1	Random table	Central/pharmacy	1	1	ITT	1
10	Mendell JR, 2013	*Ann Neurol*	Multi	U.S.	Both	Medicine	12	Positive	0	1	0	0	1	1	ITT	?
11	Pa J, 2013	*Ann Neurol*	Single	U.S.	Both	Medicine	27	Positive	0	1	Computer	Central/pharmacy	1	0	PPA	1
12	Ramos-Murguialday A, 2013	*Ann Neurol*	Single	Germany	Public	Rehabilitation	32	Positive	0	1	0	Others	1	1	PPA	1
13	Dorsey ER, 2008	*Arch Neurol*	Multi	U.S.	Public	Medicine	316	No difference	1	1	Computer	Central/pharmacy	1	1	ITT	1
14	Fleisher AS, 2008	*Arch Neurol*	Multi	U.S.	Industry	Medicine	51	Positive	0	1	0	0	1	?	ITT	1
15	Gunzler SA, 2008	*Arch Neurol*	Single	U.S.	Both	Medicine	14	Negative	1	1	0	0	1	?	PPA	1
16	Martin BK, 2008	*Arch Neurol*	Multi	U.S.	Public	Medicine	2528	Negative	1	1	Computer	Others	1	?	ITT	1
17	Rascol O, 2008	*Arch Neurol*	Multi	France	Industry	Medicine	254	Positive	1	1	Computer	Central/pharmacy	1	?	ITT	1
18	Welter M-L, 2008	*Arch Neurol*	Single	France	Public	Others	3	Positive	0	1	0	0	1	1	0	?
19	Dorsey ER, 2013	*JAMA Neurol*	Multi	U.S.	Both	Others	20	Positive	1	1	Random table	0	0	0	0	?
20	Friedman SD, 2013	*JAMA Neurol*	Single	U.S.	Public	Medicine	30	Positive	0	1	0	0	1	?	0	?
21	Dorsey ER, 2013	*JAMA Neurol*	Multi	U.S.	Both	Medicine	403	Negative	1	1	Computer	Others	1	?	ITT	1
22	Hanson AJ, 2013	*JAMA Neurol*	Single	U.S.	Public	Others	47	Positive	0	1	0	0	1	1	0	?
23	Shulman LM, 2013	*JAMA Neurol*	Single	U.S.	Public	Rehabilitation	80	Positive	0	1	Computer	0	1	?	?	1
24	Lewis RA, 2013	*JAMA Neurol*	Multi	U.S.	Public	Medicine	110	Positive	1	1	Computer	Central/pharmacy	1	?	?	1
25	Okun MS, 2013	*JAMA Neurol*	Single	U.S.	Public	Others	5	Positive	0	1	0	0	1	?	0	?
26	Walczak A, 2013	*JAMA Neurol*	Single	Poland	None	Medicine	30	Positive	0	1	0	0	1	1	0	?
27	Sandercock P, 2013	*Lancet Neurol*	Multi	U.S.	Public	Medicine	3035	Positive	0	1	Computer	0	0	0	PPA	1
28	Adelson PD, 2013	*Lancet Neurol*	Multi	U.S.	Public	Others	77	Negative	1	1	Computer	0	1	?	ITT	1
29	Anderson CS, 2008	*Lancet Neurol*	Multi	Australia	Public	Others	404	Positive	1	1	Computer	0	1	1	ITT	1
30	Backonja M, 2008	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	402	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1

PPA, per-protocol analysis, ITT, intention-to-treat.
1 = at low risk of bias, 0 = at high risk of bias, ? = unclear risk of bias.

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Supplementary Table 3. Continued

No.	Author/ Year	Journal	Single/ Multicenter	Country	Conflicts of Interest Statements	Type of Interventions	No. of Patients	Primary Outcome Explicitly Stated	Sample Size Calculation	Baseline Present	Generation of Allocation	Concealment of Allocation	Blinding: Any Type of Blinding	Blinding of Outcome Assessment	Selective Reporting	Incomplete Outcome Data
31	Bentham P, 2008	*Lancet Neurol*	Multi	U.S.	Public	Medicine	310	Negative	1	1	Computer	0	0	0	ITT	1
32	Boxer AL, 2013	*Lancet Neurol*	Multi	U.S.	Public	Medicine	81	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
33	Cudkowicz ME, 2013	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	943	Negative	1	1	Computer	0	1	?	ITT	1
34	Dauvilliers Y, 2013	*Lancet Neurol*	Multi	France	Industry	Medicine	95	Positive	1	1	Computer	Others	1	1	ITT	1
35	Davis SM, 2008	*Lancet Neurol*	Multi	Australia	Public	Medicine	101	Positive	1	1	Computer	Others	1	1	PPA	1
36	Dichgans M, 2008	*Lancet Neurol*	Multi	Germany	Public	Medicine	168	Negative	1	1	Computer	0	1	?	ITT	1
37	Diener HC, 2008	*Lancet Neurol*	Multi	Germany	Industry	Medicine	20332	No difference	0	1	Computer	0	1	?	ITT	1
38	Dodel R, 2013	*Lancet Neurol*	Multi	Germany	Industry	Medicine	58	Negative	1	1	Computer	Central/pharmacy	1	?	ITT	1
39	Eckstein HH, 2008	*Lancet Neurol*	Multi	Germany	Public	Surgery	1214	Positive	1	1	Computer	0	0	0	ITT	1
40	Ederle J, 2013	*Lancet Neurol*	Multi	U.S.	Public	Surgery	1036	Positive	0	1	Computer	0	0	0	PPA	1
41	Engström M, 2008	*Lancet Neurol*	Multi	Sweden	Both	Medicine	839	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1
42	Ginsberg MD, 2013	*Lancet Neurol*	Multi	U.S.	Both	Medicine	841	Negative	1	1	Computer	Others	1	0	ITT	1
43	Hauser RA, 2103	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	393	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1
44	Huang Y, 2008	*Lancet Neurol*	Multi	China	Both	Medicine	740	Positive	0	1	Computer	Central/pharmacy	1	1	ITT	1
45	Hugh FG, 2008	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	117	Positive	1	1	Computer	Others	1	0	ITT	1
46	Kirton A, 2008	*Lancet Neurol*	Multi	Canada	Public	Others	10	Positive	1	1	0	Central/pharmacy	1	1	PPA	1
47	Lannfelt L, 2008	*Lancet Neurol*	Multi	Sweden	Industry	Medicine	78	Positive	0	1	Computer	Central/pharmacy	1	?	ITT	1
48	Ljøstad U, 2008	*Lancet Neurol*	Multi	Norway	Public	Medicine	118	Positive	1	1	Computer	Central/pharmacy	1	1	PPA	1
49	Mas J-L, 2008	*Lancet Neurol*	Multi	France	Public	Surgery	527	Positive	1	1	Computer	Others	1	?	ITT	1
50	Meyer BC, 2008	*Lancet Neurol*	Multi	U.S.	Public	Others	234	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1
51	Mikol DD, 2008	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	764	No difference	1	1	Computer	0	0	0	ITT	1
52	Miller TM, 2013	*Lancet Neurol*	Multi	U.S.	Both	Medicine	22	Positive	0	1	Computer	Central/pharmacy	1	?	?	0
53	Morrison KE, 2013	*Lancet Neurol*	Multi	U.S.	Public	Medicine	214	Negative	1	1	Computer	Others	1	0	ITT	1
54	Neal EG, 2008	*Lancet Neurol*	Multi	U.S.	Public	Others	145	Positive	1	1	Computer	0	0	0	ITT	1
55	Odekerken VJJ, 2013	*Lancet Neurol*	Multi	Netherlands	Public	Surgery	128	No difference	1	1	Computer	Central/pharmacy	1	?	ITT	1
56	Peters R, 2008	*Lancet Neurol*	Multi	U.S.	Public	Others	3336	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
57	Schapira AHV, 2013	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	535	Negative	1	1	Computer	Others	1	?	?	1
58	Scott PA, 2013	*Lancet Neurol*	Multi	U.S.	Public	Others	40823	Negative	1	1	Computer	0	1	0	ITT	1
59	Segal BM, 2008	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	249	Negative	1	1	Computer	0	1	?	ITT	1
60	Selmaj K, 2013	*Lancet Neurol*	Multi	Poland	Industry	Medicine	297	Positive	1	1	Computer	Others	1	?	?	1
61	Stingele R, 2008.	*Lancet Neurol*	Multi	Germany	Industry	Surgery	1196	Positive	0	1	0	0	0	0	ITT	1
62	Trenkwalder C, 2008.	*Lancet Neurol*	Multi	Germany	Industry	Medicine	458	Positive	1	1	Computer	Central/pharmacy	1	?	ITT	1
63	Trenkwalder C, 2013	*Lancet Neurol*	Multi	Germany	Industry	Medicine	495	Positive	1	1	Computer	Central/pharmacy	1	1	?	1

64	Vaart TVD, 2013	*Lancet Neurol*	Multi	Netherlands;	Public	Medicine	84	Negative	1	1	Computer	Others	1	?	ITT	1
65	Wilcock GK, 2008	*Lancet Neurol*	Multi	U.S.	Industry	Medicine	210	Positive	1	1	Computer	0	1	0	ITT	1
66	Witt K, 2008	*Lancet Neurol*	Multi	Germany	Public	Surgery	156	Positive	0	1	0	0	0	0	PPA	1
67	Wolf S, 2008	*Lancet Neurol*	Multi	U.S.	Public	Rehabilitation	222	Positive	0	1	0	0	1	?	PPA	1
68	Zajicek J, 2013	*Lancet Neurol*	Multi	U.S.	Public	Medicine	498	Negative	1	1	Computer	Central/pharmacy	1	0	ITT	1
69	Sanders DB, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	80	Negative	1	1	Computer	0	1	1	ITT	1
70	Afridi SK, 2013	*Neurology*	Single	U.S.	None	Medicine	30	Positive	0	1	Computer	Central/pharmacy	1	?	?	1
71	André-Obadia N, 2008	*Neurology*	Single	France	Public	Others	28	Positive	0	1	Computer	Central/pharmacy	1	?	0	?
72	Arnold AC, 2013	*Neurology*	Single	U.S.	Public	Medicine	24	Positive	1	1	Computer	Central/pharmacy	1	?	PPA	1
73	Aziz NA, 2008	*Neurology*	Multi	Netherlands;	Public	Others	517	Positive	0	1	0	0	0	0	?	1
74	Birnbaum G, 2008	*Neurology*	Single	U.S.	Industry	Medicine	26	Negative	0	1	0	Central/pharmacy	1	1	?	1
75	Cardenas DD, 2013	*Neurology*	Multi	U.S.	Industry	Medicine	220	Positive	1	1	Computer	Central/pharmacy	1	?	ITT	1
76	Chancellor MB, 2013	*Neurology*	Multi	U.S.	Industry	Medicine	416	Positive	0	1	Computer	Others	1	?	ITT	1
77	Chiaravallot ND, 2013	*Neurology*	Single	U.S.	Public	Others	86	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1
78	DeGiorgio CM, 2013	*Neurology*	Multi	U.S.	Public	Rehabilitation	50	Positive	1	1	Computer	Central/pharmacy	1	?	ITT	1
79	Dodge HH, 2008	*Neurology*	Multi	U.S.	Public	Medicine	122	Positive	1	1	Minimization	Real-time	1	1	ITT	1
80	Edwards JD, 2013	*Neurology*	Multi	U.S.	Public	Rehabilitation	87	Positive	1	1	Computer	0	0	0	?	1
81	Fallon BA, 2008	*Neurology*	Multi	U.S.	Public	Medicine	45	Positive	1	1	Computer	Others	1	?	ITT	1
82	Faught E, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	537	Positive	1	1	Computer	Central/pharmacy	1	?	?	1
83	Fazekas F, 2008	*Neurology*	Multi	Austria	Industry	Medicine	127	Negative	1	1	Computer	Central/pharmacy	1	?	ITT	1
84	Geschwind GF, 2013	*Neurology*	Single	U.S.	Industry	Medicine	54	Negative	1	1	Computer	0	1	?	ITT	1
85	Glauser T, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	139	Positive	1	1	Computer	0	1	?	ITT	1
86	Goldstein LB, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	4731	Positive	0	1	0	0	1	?	ITT	0
87	Goodman AD, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	206	Positive	1	1	0	0	1	1	ITT	1
88	Haubenberger D, 2013	*Neurology*	Single	U.S.	Both	Medicine	19	Positive	1	1	0	0	1	?	?	1
89	Ho TW, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	420	Positive	0	1	0	Central/pharmacy	1	1	PPA	1
90	Horton L, 2013	*Neurology*	Single	U.S.	Public	Medicine	22	Positive	0	1	0	0	1	1	?	1
91	Katzenschlager R, 2008	*Neurology*	Multi	U.S.	Not specific	Medicine	782	Negative	0	1	Random table	0	0	0	ITT	1
92	Léger, J-M, 2013	*Neurology*	Multi	France	Industry	Medicine	54	Positive	1	1	Computer	Central/pharmacy	1	1	PPA	1
93	Malow BA, 2008	*Neurology*	Multi	U.S.	Public	Others	35	Positive	0	1	Computer	Central/pharmacy	1	0	?	1
94	Marqu FGA, 2013	*Neurology*	Single	France	Public	Surgery	19	Positive	1	1	0	Central/pharmacy	1	?	0	?
95	Masur D, 2013	*Neurology*	Multi	U.S.	Public	Others	446	Positive	1	1	0	Central/pharmacy	1	1	ITT	1
96	Moore AP, 2008	*Neurology*	Single	U.S.	Industry	Medicine	64	Negative	1	1	Computer	Others	1	1	ITT	1
97	Nakasujja N, 2013	*Neurology*	Single	Uganda	Public	Medicine	73	Negative	1	1	Random table	0	1	?	ITT	1
98	Noachtar S, 2008	*Neurology*	Multi	Germany	Industry	Medicine	122	Positive	1	1	Computer	0	1	?	ITT	1

PPA, per-protocol analysis, ITT, intention-to-treat.
1 = at low risk of bias, 0 = at high risk of bias, ? = unclear risk of bias.

Continues

Supplementary Table 3. Continued

No.	Author/ Year	Journal	Single/ Multicenter	Country	Conflicts of Interest Statements	Type of Interventions	No. of Patients	Primary Outcome Explicitly Stated	Sample Size Calculation	Baseline Present	Generation of Allocation	Concealment of Allocation	Blinding: Any Type of Blinding	Blinding of Outcome Assessment	Selective Reporting	Incomplete Outcome Data
99	Kaufmann LN, 2013	*Neurology*	Single	U.S.	Public	Medicine	12	Positive	0	1	Computer	0	1	?	?	1
100	Okai D, 2013.	*Neurology*	Single	U.S.	Public	Others	44	Positive	1	1	Random table	0	0	0	ITT	1
101	Pandian JD, 2013	*Neurology*	Multi	India	Public	Others	162	Positive	1	1	Computer	Others	1	1	ITT	1
102	Penisson-Besnier I, 2008	*Neurology*	Multi	France	Public	Medicine	75	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
103	Pinã-Garza JE, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	38	Positive	1	1	0	Central/pharmacy	1	?	ITT	1
104	Rabadi MH, 2008	*Neurology*	Single	U.S.	Public	Others	116	Positive	1	1	0	Central/pharmacy	1	?	?	1
105	Reger MA, 2008	*Neurology*	Single	U.S.	Both	Medicine	25	Positive	0	1	Random table	Others	1	1	?	1
106	Sanders DB, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	176	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
107	Saxby BK, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	257	Negative	1	1	Computer	Central/pharmacy	1	?	ITT	1
108	Schifitto G, 2008	*Neurology*	Multi	U.S.	Not specific	Medicine	361	Negative	0	1	0	0	1	?	?	0
109	Schoenen J, 2013	*Neurology*	Multi	Belgium	Both	Others	67	Positive	1	1	0	Central/pharmacy	1	1	ITT	0
110	Sevigny JJ, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	563	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
111	Shirota Y, 2013	*Neurology*	Multi	Japan	Public	Surgery	106	Positive	1	1	Computer	Central/pharmacy	1	1	ITT	1
112	Silberstein SD, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	576	Positive	1	1	Computer	Central/pharmacy	1	?	ITT	1
113	Silberstein S, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	170	Negative	1	1	Computer	Central/pharmacy	1	?	ITT	1
114	Silverberg GD, 2008	*Neurology*	Multi	U.S.	Public	Others	215	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
115	Simioni S, 2013	*Neurology*	Multi	Switzerland	Public	Medicine	17	Positive	1	1	0	Central/pharmacy	1	?	?	1
116	Simpson DM, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	307	Positive	1	1	0	0	1	?	ITT	1
117	Skura CL, 2008	*Neurology*	Single	U.S.	Public	Medicine	14	Positive	0	1	0	Central/pharmacy	1	?	?	1
118	Sorenson EJ, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	330	Negative	1	1	Computer	Central/pharmacy	1	0	ITT	1
119	Squitieri F, 2013	*Neurology*	Multi	Italy	Industry	Medicine	437	Positive	0	1	0	0	1	?	?	1
120	Stacy M, 2008	*Neurology*	Multi	U.S.	Industry	Medicine	395	Positive	1	1	0	0	1	?	ITT	1
121	Storch A, 2013	*Neurology*	Single	Germany	Industry	Medicine	40	Positive	1	1	0	Central/pharmacy	1	1	ITT	1
122	Tzourio C, 2008	*Neurology*	Multi	France	Public	Others	5671	Positive	0	1	0	0	1	?	?	0
123	van de Rest O, 2008	*Neurology*	Single	Netherlands	Public	Medicine	302	Negative	1	1	Computer	Central/pharmacy	1	1	ITT	1
124	Winblad B, 2008	*Neurology*	Multi	Sweden	Industry	Medicine	2048	Negative	1	1	0	Central/pharmacy	1	1	ITT	1
125	Cappelletti M, 2013	*J NEUROSCI*	Single	U.S.	Public	Medicine	40	No difference	0	0	0	0	1	?	0	?
126	Casey KF, 2013	*J NEUROSCI*	Single	Canada	Public	Medicine	24	Positive	0	0	0	0	1	?	0	?
127	Eippert F, 2008	*J NEUROSCI*	Single	Germany	Public	Medicine	32	Positive	0	0	0	0	1	?	0	?
128	Furmark T, 2008	*J NEUROSCI*	Single	Sweden	Both	Medicine	25	Positive	0	1	0	0	1	1	0	?
129	Gais S, 2008	*J NEUROSCI*	Single	Germany	Public	Medicine	26	No difference	0	0	0	0	1	0	0	?
130	Gießing C, 2013	*J NEUROSCI*	Single	U.S.	Public	Medicine	18	Positive	0	1	0	0	1	?	0	?

131	Hébert S, 2013	*J NEUROSCI*	Single	Canada	Public	Medicine	116	Positive	0	0	0	0	0	0	0	?
132	Hofstetter S, 2013	*J NEUROSCI*	Single	Israel	Public	Medicine	70	Positive	0	0	Computer	0	0	0	0	?
133	Iuculano T, 2013	*J NEUROSCI*	Single	U.S.	Public	Medicine	19	Positive	0	0	0	0	0	0	0	?
134	Kometer M, 2013	*J NEUROSCI*	Single	Switzerland	Public	Medicine	17	Positive	0	1	0	0	1	?	0	?
135	Lee TG, 2013	*J NEUROSCI*	Multi	U.S.	Public	Medicine	35	Positive	0	0	0	0	0	0	0	?
136	Phan KL, 2008	*J NEUROSCI*	Single	U.S.	Public	Medicine	16	Positive	0	0	0	0	1	?	0	?
137	Sehm B, 2013	*J NEUROSCI*	Single	Germany	Public	Medicine	36	Positive	0	1	0	0	1	?	0	?
138	Wang AL, 2013	*J NEUROSCI*	Single	U.S	Public	Others	71	Positive	0	1	0	0	0	0	0	?

PPA, per-protocol analysis, ITT, intention-to-treat.
1 = at low risk of bias, 0 = at high risk of bias, ? = unclear risk of bias.