RESEARCH ARTICLE

Outcome Reporting Bias in Clinical Trials Researching Disease-Modifying Therapy in Patients With Multiple Sclerosis

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Abstract

Background and Objectives

Outcome reporting bias occurs when publication of trial results is dependent on clinical significance, thereby threatening the validity of trial results. Research on immunomodulatory drugs in multiple sclerosis has thrived in recent years. We aim to comprehensively examine to what extent outcome reporting bias is present in these trials and the possible underlying factors.

Methods

We identified clinical trials evaluating the efficacy and safety of immunomodulatory drugs in patients with multiple sclerosis (MS) registered in ClinicalTrials.gov after September 2007 and completed before the end of 2018. Information about study design, type of funding, and primary and secondary outcome measures was extracted from the registry. Timing of registration in relation to study initiation and subsequent amendments to the planned outcomes were reviewed. Publications related to these trials were identified in several bibliographic databases using the trial registration number. Registered primary and secondary outcomes were recorded for each trial and compared with outcomes in the publication describing the main outcomes of the trial.

Results

A search of ClinicalTrials.gov identified 535 eligible registered clinical trials; of these, 101 had a matching publication. Discrepancies between registered and published primary and secondary outcomes were found in 95% of the trials, including discrepancies between the registered and published primary outcomes in 26 publications. Forty-four percent of the published secondary outcomes were not included in the registry. A similar proportion of registered and non-registered reported primary efficacy outcomes were positive (favoring the intervention). Nonindustry-funded and open-label trials in MS were more prone to selective primary outcome reporting, although these findings did not reach statistical significance. Only two-thirds of the trials were registered in ClinicalTrials.gov before the trial start date, and 62% of trials made amendments in registered outcomes during or after the trial period.

Discussion

Selective outcome reporting is prevalent in trials of disease-modifying drugs in people with MS. We propose methods to diminish the occurrence of this bias in future research.

Background

Evidence-based medicine is dependent on the quality and accuracy of clinical trials researching interventions, which may be hampered by different types of biases. Publication bias arises when the publication of trials depends on the favorability and significance of their results.[1] Outcome reporting bias occurs when predefined trial outcomes in study protocols are selectively or

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Glossary

FDAAA = Food and Drug Administration Amendments Act; **MS** = multiple sclerosis.

incorrectly published, for example, the inclusion of new outcomes, omission or substitution of predefined outcomes concerning time point evaluation, or evaluative tests. Prior studies show that statistically significant results are more often completely reported than nonsignificant results.[1] These biases pose a serious threat to health care because biased research results concerning safety and effectivity may lead to overestimation or underestimation of treatment effects.

Prospective clinical trial registration may mitigate publication and outcome reporting bias and enhance the reliability and transparency of clinical research. The World Health Organization has identified several primary clinical trial registries that meet certain criteria for content, quality and validity, accessibility, unique identification, technical capacity, and administration and several data providers that are responsible for a database that is used by 1 or more registries. One such data provider is the NIH's international online trial database ClinicalTrials.gov.[2] In 2004, the International Committee of Medical Journals issued a policy requiring prospective registration of clinical trials as a precondition for manuscript submission.[3] Since September 27, 2007, the Food and Drug Administration Amendments Act (FDAAA) requires all clinical trials studying medication, behavioral interventions, or medical devices to register their trial (including predefined outcome measures) within 21 days after enrollment of the first trial participant.[4] Currently, ClinicalTrials.gov is the largest international online database of clinical trial studies, with more than 440,000 trials registered as of April 2023.[5] The ClinicalTrials.gov registration includes a time-stamped summary of key trial protocol details, including predefined outcome measures, although not all components present in a complete protocol are obligatory in a trial registration.

Although more than a decade has passed with mandatory trial registration for studies pursuing drug approval, outcome reporting bias is still widely present in medical research.[6-12] Research into therapies of multiple sclerosis (MS) is well-funded and rapidly expanding with new drug options appearing on the worldwide market nearly annually. A recent study looking at publication bias in phase 3–4 trials of immunomodulatory and symptomatic drugs for MS found that a third of trials did not publish their results in peer-reviewed journals.[13] The occurrence of outcome reporting bias in this field, however, has not been previously reported. The objective of this study was to examine the prevalence of outcome reporting bias in trials of disease-modifying medications for MS and the factors that contribute to selective reporting of outcome measures.

Methods

Selection of Trials and Publications

Two reviewers (C.L. and S.v.A.) independently searched ClinicalTrials.gov on January 22, 2022, for interventional phase 1b–4 clinical trials researching drug efficacy and safety/tolerability endpoints of MS drugs with status "completed," "prematurely ended," or "unknown." This was performed using the search term "multiple sclerosis" and the inclusion and exclusion criteria listed in Table 1. We included trials submitted to ClinicalTrials.gov after September 1, 2007 because the FDAAA started requiring prospective trial submission to the registry on this date. Trials were included if they were completed before December 31, 2018, to ensure sufficient time interval for manuscript publication. Discrepancies in trial selection

Table 1 Overview of Trial Inclusion and Exclusion Criteria in the ClinicalTrials.gov Search

Inclusion criteria	Exclusion criteria
Interventional trial researching disease-modifying treatment	Symptomatic therapy
Patients with multiple sclerosis (relapsing-remitting, secondary progressive, primary progressive, and all MS types) and clinically isolated syndrome	Exacerbation therapy
Population of adults and/or children	Over-the-counter therapy
Phase 1b–4 trial	Outcomes exclusively focusing on side-effects, laboratory results, and biomarkers
Registration to ClinicalTrials.gov after September 1, 2007	Nonpharmacological intervention (e.g., procedure, device, behavioral, or psychological)
Completion of trial before December 31, 2018	Study population limited to patients with optic neuritis
	Study population not limited to population with MS
	Study population with healthy controls
	Ongoing, terminated or withdrawn trial

between the 2 researchers were resolved by a consensus meeting with a third reviewer (J.K.).

Matching publications of the trials were identified by searching PubMed, Excerpta Medica dataBASE (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar using the ClinicalTrials.gov Identifiers (National Clinical Trial numbers) on February 15, 2022. If this did not result in a matching publication, a search was performed using the trial registration title. A repeated search for new publications was performed on 6 March 2023 by a second reviewer. Non-English publications were excluded from analysis. If no publication was found in any of the databases, the primary investigators of the trials were contacted to inquire whether a peer-reviewed publication was available. Trials without publication are separately reported in eTable 2 (links.lww.com/WNL/D444). One publication per trial registration was selected; if multiple publications were available for a trial, we included the publication most coherent to the predefined study design and reporting the main outcomes of the trial.

Standard Protocol Approvals

Because this research presents prepublished scientific data and no human participants were involved, it is exempt from ethics board review approval.

Data Retrieval

Two researchers independently abstracted the trial descriptions from the ClinicalTrials.gov registry including information on study design; date of trial registration, date of initiation, and completion dates; study phase; study aim (clinical, safety, patient satisfaction, or multiple); drug name; comparator group(s); masking; subtype of MS (all MS types, relapsing-remitting MS, primary or secondary progressive MS, or clinically isolated syndrome); and type of funding (industry funded or non-industry funded, e.g., university or private institute). Study locations stated at ClinicalTrials.gov and in the publication were reviewed to determine whether trials were multicenter and international. We reviewed whether the outcome measures had been changed after trial registration, with inclusion of new parameters or omission of outcomes from an earlier version. Any modifications to the registered outcomes specifying the method of aggregation (e.g., EDSS for functional neurologic outcome) in a later version were not deemed as substantial modifications. Timing of latest update of registered outcome section was recorded. Outcome measures in ClinicalTrials.gov registrations noted as "other outcomes" were deemed "secondary outcomes."

Outcomes reported in the publication of the trial were independently abstracted and evaluated for inconsistencies with predefined method and outcome. Data from outcome amendments in the registration were prioritized over data from earlier versions when comparing these with published outcomes. Disagreements were resolved by consensus after the abstractors reviewed the articles a second time. The Outcome Reporting Bias In Trials (ORBIT) classification system was used to identify missing or incomplete outcome reporting in efficacy outcomes, comparing published and predefined outcome measures on principality (whether outcomes were changed from primary to secondary outcome or vice versa), outcome domain, specific measure (e.g., clinical, laboratory, or radiologic test), and time point of outcome assessment.[14] We reviewed the publications to determine if outcomes were measured and statistically analyzed conform the registered planning. If a nonspecific outcome (e.g., fatigue) was adequately specified in the publication through the method of assessment (e.g., using the Fatigue Severity Scale), this was not considered as nonadherence to the registered outcome. Nonpredefined published secondary outcomes indicated as "post hoc" were recorded but not deemed as nonadherence to the registry. Post hoc primary outcomes stated in the publications were, nonetheless, regarded as a nonregistered primary outcomes. The direction of primary efficacy outcome results was defined as positive or negative in terms of the null hypothesis, regardless of whether the trials were investigating superiority, noninferiority, or equivalence of interventions. We extracted publication date, ultimate sample size, and journal impact factor and H-index of all trials according to the Journal Citation Reports.

Statistical Analysis

The primary objective of our study was to evaluate adherence in publications to registered primary and secondary outcome measures and to identify possible determinants of nonadherence to reporting of registered primary outcome measures, including study characteristics and directionality of results. Descriptive data were presented as frequencies with percentages or mean values with SD. Quantitative data were presented as median, accompanied by a 25th percentile (P_{25}) and a 75th percentile (P_{75}). A χ^2 test was used to examine differences in the proportion of published favorable outcomes (in terms of the total of efficacy outcomes) when comparing the predefined and nonpredefined outcomes in the published studies. This same statistical test was used to evaluate the relationship between adherence to registered primary outcomes and the source of study funding (industry or non-industry), study design (open-label or randomized controlled trial), use of study name or acronym, and marketing-registered status of trial medication. Influence of publication year, trial duration, sample size, journal impact factor and H-index, and number of predefined outcome measures on adherence to registered primary outcomes was tested by a bivariate logistic regression, thus calculating odds ratio (OR) and 95% confidence intervals (CIs). In the case of asymmetrical distribution of data, the predictor variable was log transformed for this statistical analysis, which was performed for the variables patient enrollment and journal impact factor. A Pearson correlation (r) was used to determine the correlation between the number of predefined primary outcomes and the number of deviations observed from the registered primary outcomes in the publications. Significance threshold for the statistical tests was set at 0.05. IBM SPSS software was used for statistical analyses.

Data Availability

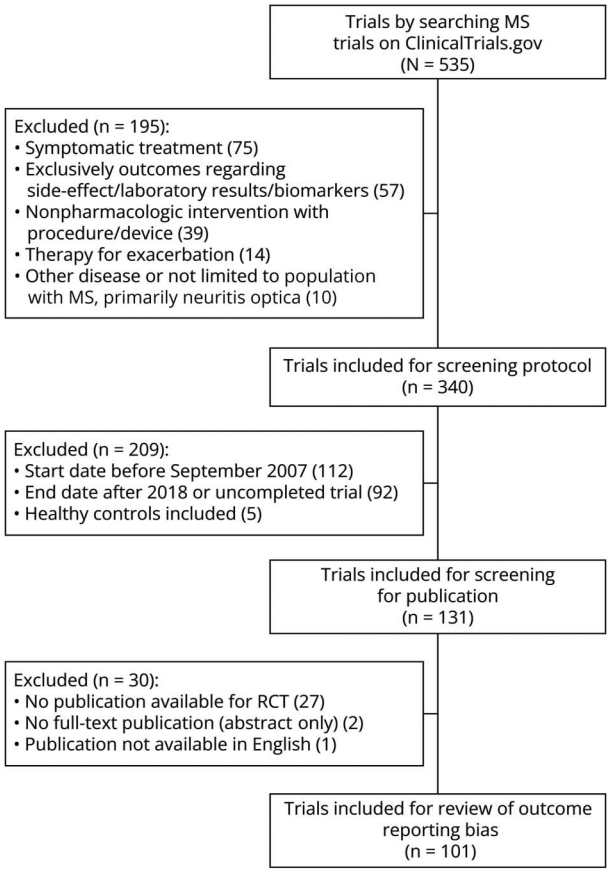
Data are available on reasonable request.

Results

The search of ClinicalTrials.gov identified 535 eligible clinical trials (Figure). Only trials investigating clinical efficacy and safety effects of immunomodulatory drugs were included. A search of the bibliographic databases was performed for 131 trials to identify peer-reviewed publications. These included 7 trials for which we retrieved a matching publication through enquiry of the principal investigator and sponsor. Twenty-nine trials were excluded for further analyses because no (full-text) peer-reviewed publication was available; 1 additional study was published in Russian and therefore excluded. As a result, 101 trials were reviewed for the occurrence of outcome reporting bias (eTable 1, links.lww.com/WNL/D443). The studies without a matching (full-text) peer-reviewed publication are listed in eTable 2 (links.lww.com/WNL/D444).

Clinical trial characteristics are described in Table 2. Most trials were of randomized controlled design (63%), enrolled patients with relapsing-remitting MS (68%), were multicenter (80%), and industry funded (75%). Patient enrollment varied between 4 and 4,125 patients, with a median of 175 patients per trial (SD 596). A total of 46 different immunomodulatory drugs were investigated. The median trial duration was 37.0 months (P_{25} 25.5, P_{75} 48.1), and the median time from trial completion to publication was 27.6 months (P_{25} 20.7, P_{75} 40.0). Most studies had a single primary publication of the trial results (57%), but the number of publications per trial ranged from 1 to 14.

Figure Flowchart of Trial Selection and Exclusion Criteria



Registration of Trial

Overall, 69 trials were registered in ClinicalTrials.gov before or within 21 days after the study start date (68%), and these are considered as prospectively registered. A higher proportion of studies published between 2012 and 2017 were registered retrospectively compared with those published in later years (37% vs 24%, $p = 0.28$). Among trials that were registered retrospectively, the median time between trial initiation and registration was 4 months (range 1–40 months). Overall, 62% of trials made 1 or more substantial amendments to the registered outcomes after their initial submission to ClinicalTrials.gov. Among prospectively registered trials, 51 (74%) had changes in registered outcome measures; on average 7 changes per registration, including the addition of primary outcomes (in 13 trials); omission of primary outcomes (in 9 trials); addition of secondary outcomes (in 44 trials); and omission of secondary outcomes (in 22 trials). In prospectively registered trials, the median time from trial initiation to submission of amendments in the outcome section was 58 months (range 3–167 months). In 40 of these trials (78%), changes were made after trial completion. Changes to the registration among prospectively registered trials were equally prevalent in earlier (2012–2017) vs later published studies (76% vs 71%). Of the 32 trials that registered to ClinicalTrials.gov after trial initiation, outcome section was later updated in 12 trials (38%, median time from trial initiation to changes in outcome section of 48 months, range 6–62 months), in 10 trials after trial completion.

Discrepancies in Registered and Published Primary Outcomes

Overall, 96 of the 101 trials (95%) had discrepancies between the registered and the published outcome measures. Four of the 5 trials that fully adhered to the registered details were registered on ClinicalTrials.gov before the study initiation date. The single study that fully adhered to the registered details but that was registered retrospectively (with a delay of 2 months) added 10 secondary outcome measures in the registration after study initiation. In 26 publications (26%), 1 or multiple discrepancies between registered and published primary outcomes were found (Table 3), including the introduction of new primary outcomes in 17 trials (total of 24 new primary outcomes, including 63% efficacy parameters) and dismissal of registered primary outcomes in 11 trials (total of 41 nonpublished primary outcomes). Difference in time frame of primary outcome assessment between registration and publication was seen in 4 trials. A higher proportion of the nonregistered primary efficacy outcomes in publications showed significant favorable results in comparison with the

proportion of predefined primary outcomes, but the difference was not significant (53% vs 34%, $p = 0.12$). Discrepancies in primary outcomes between the registry and the publication were more common in open-label than in blinded studies (38% vs 19%, $p = 0.06$) and in nonindustry-funded vs industry-funded trials (40% vs 21%, $p = 0.07$), but neither finding reached statistical significance. Having more registered primary outcomes was associated with nonadherence to these outcomes in the publications ($r = 0.82$, 95% CI 0.74–0.88, $p < 0.001$), most commonly leading to nonpublication of registered primary outcomes. The proportion of trials with discrepancies in the registered and published outcomes was similar among trials with single or multiple publications (29% vs 21%, $p = 0.37$). Trials investigating drugs with marketing authorization in the European Union had a slightly higher tendency to have discrepancies between registered and published primary outcomes (33% vs 23%, $p = 0.31$). Accurate publication of registered primary outcomes was not influenced by publication year (OR 0.94; 95% CI 0.79–1.13), patient enrollment (OR 1.15; 95% CI 0.75–3.08), time interval between study end date and publication (OR 1.00, 95% CI 0.97–1.03), trial duration (OR 0.98, 95% CI 0.96–1.01), or journal impact factor (OR 1.74; 95% CI 0.66–4.60). Occurrence of primary outcome reporting bias was similar in studies with an assigned trial name or acronym and in unnamed studies (27% vs 24%).

Discrepancies in Registered and Published Secondary Outcomes

Overall, 96 trials (95%) had discrepancies in registered and published secondary outcomes, with the addition of new secondary outcomes in 91 publications (median 4, range 1–16 outcomes) and dismissal of registered secondary outcomes in 47 publications (median 2, range 1–15 outcomes). In total, 44% of the total published secondary outcomes in the 101 trials were not registered in ClinicalTrails.gov. Forty-two trials (42%) did not include safety outcomes in the registration but extensively described these in the publications, in 2 trials even as nonregistered primary outcomes. In one other trial, neither the trial registration nor the subsequent publication contained any safety-related outcomes. Most of the trials lacking safety outcomes in the registration were phase 2 trials (N = 20), although 3 phase 1 trials did not specify safety outcomes in their registration. In 30% of trials, 1or more post hoc outcome or statistical analysis was published, with on average 1.7 outcomes per publication.

Discussion

Despite the implementation of FDAAA regulation in 2007 to ensure the accurate and timely registration of clinical trials, outcome reporting bias is still widely prevalent within trials researching immunomodulatory drugs for patients with MS. Although all included studies were initiated after this regulation was installed, we found that only 68% of trials were prospectively registered to ClinicalTrials.gov. We detected discrepancies between the trial registration and the publication in 95% of included trials, including nonadherence to registered primary outcomes in a quarter of the trials. Moreover, nearly half of the publications failed to publish at least 1 registered secondary outcome, and 44% of published secondary outcomes were not registered. We did not find a significant correlation between favorability of primary outcome results regarding the null hypothesis and outcome reporting bias. We did, however, detect an influence of the source of funding of the trial and trial allocation on selective outcome reporting, with a nonsignificantly higher incidence of primary outcome reporting bias in open-label and nonindustry-funded trials. The observation that industry-funded studies are less likely to exhibit selective outcome reporting aligns with previous research and could be attributed to industry's experienced data entry personnel in the registration of trials. The significant prevalence of nonregistered safety outcomes being published is another observation to further address. This phenomenon, predominantly observed in phase 2–4 trials, prompts us to consider whether the incorporation of safety outcomes in publications was more a response to editorial or reviewer requests, rather than an inherent aspect of the original objectives of these trials. We uncovered a notable frequency of amendments in registered outcomes on ClinicalTrials.gov after trial initiation, with a pronounced prevalence observed in prospectively registered trials. In most of these trials, changes occurred post trial completion. This further raises the concern of potential outcome reporting bias because these changes seem to be made after researchers had access to the data and may be selectively published to favor the researchers' hypotheses or interests.

Our study confirms previous studies that suggest that clinical trial registers alone do not eradicate outcome reporting bias, with reports in other clinical fields of discrepancies between registered and published primary outcomes in 14%–76% of the trials.[9,14-22] To attain the potential of these registries and safeguard the credibility and integrity of study findings, all stakeholders should enforce compliance with prospective registration and publication of registered outcomes. First, trialists are responsible for prospective and accurate registration of their studies, with timely submission of amendments to registries if these are warranted during the trial duration. Amendments in registered outcomes after study initiation should be justified in the publication of the clinical trials, to enable a critical evaluation of their validity. Within our cohort, this was seldom detected. Furthermore, registries are responsible for demanding justification from researchers for changes to the registered outcomes after trial initiation. Medical research committees and journal editors are henceforth responsible for ensuring compliance between registries and publications and must be vigilant for discrepancies in registered and published outcomes in the process of accepting publications. We propose the implementation of more homogenous registration of drug trial. The development of a standardized outcome set of drug safety and

Table 2 Overview of Trial Characteristics

Type of disease, n (%)	
Relapsing-remitting MS	69 (68)
Primary or secondary progressive MS	12 (12)
Both relapsing-remitting and progressive MS	15 (15)
Clinically isolated syndrome	5 (5)
Age group, n (%)	
Adults	98 (97)
Children	1 (1.0)
Both adults and children	2 (2.0)
Trial phase, n (%)	
Phase 1b	13 (13)
Phase 2/2b	47 (47)
Phase 3	26 (26)
Phase 4	15 (15)
Allocation, n (%)	
Randomized controlled trial	64 (63)
Open-label trial	37 (37)
Masking, n (%)	
None	30 (30)
Single	8 (7.9)
Double	16 (16)
Triple	13 (13)
Quadruple	34 (34)
Comparator group, n (%)	
Placebo	50 (49)
Active agent	8 (7.9)
None (dose-finding or open-label design)	34 (34)
Both placebo and active agent	9 (8.9)
Study location(s), n (%)	
Monocenter	20 (20)
Multicenter	81 (80)
National	44 (44)
International	57 (56)
Type of sponsor, n (%)	
Industry	76 (75)
University/hospital	19 (19)
National institute	6 (5.9)
Publication year, n (%)	
2012–2017	60 (59)
2018–2022	41 (41)
Immunomodulatory drug, n (%)	
Fingolimod	10 (9.8)
Natalizumab	8 (7.8)
Interferon beta	7 (6.9)
Stem cell therapy	6 (5.9)
Glatirameer acetate	5 (4.9)
Teriflunomide	5 (4.9)
Dimethylfumarate	5 (4.9)
Daclizumab	4 (3.9)
Laquinimod	4 (3.9)
Temelimab	2 (2.0)
Ozanimod	3 (2.9)
Vitamin D	3 (2.9)
Alemtuzumab	2 (2.0)
Amiselimod	2 (2.0)
Cladribine	2 (2.0)
Ofatumumab	2 (2.0)
Rituximab	2 (2.0)
Siponimod	2 (2.0)
Ocrelizumab	1 (1.0)
Ublitiximab	1 (1.0)
Ponesimod	1 (1.0)
Other drugs	25 (25)
Primary trial drug, n (%)	
Marketing authorization valid in European Union (at trial initiation)	27 (27)
Under investigation/nonauthorized for marketing in European Union (at trial initiation)	74 (73)
Study aim, n (%)	
Efficacy	69 (68)
Safety	21 (21)
Patient satisfaction	6 (5.9)
Both safety and efficacy	5 (5.0)
ClinicalTrials.gov registration, n (%)	
Prospective	69 (68)
Retrospective	32 (32)
No. of primary publication(s), n (%)	
Single	58 (57)
Multiple	43 (43)

Table 3 Overview of Discrepancies Between Registered and Published Primary and Secondary Outcomes

	No. of trials with discrepancies (%)	No. of discrepancies (% of total predefined or published outcomes)	Mean no. of discrepancies per included trial (N = 101)
Primary outcomes			
Registered outcome omitted in publication	11 (11)	41/206 (20 predefined)	0.45 (SD 1.8)
Published outcome not predefined in registry	17 (17)	24/189 (13 published)	0.24 (SD 0.6)
Secondary outcomes			
Registered outcome omitted in publication	47 (47)	146/750 (19 predefined)	1.4 (SD 2.8)
Published outcome not predefined in registry	91 (90)	481/1,085 (44 published)	4.8 (SD 3.8)

efficacy parameters within the field of MS will help reduce outcome reporting bias and ameliorate the quality of future meta-analyses, as trial outcomes become more uniform and reproducible. Core outcome sets (COS) are now increasingly assembled and reviewed within various fields of medicine. The implementation of an internationally accepted COS within MS research would benefit future research.

Strengths of our study are the large number of registered trials and inclusion of high-impact and low-impact factor journals. In cases where no matching publication could be retrieved for a trial registration, we contacted the primary investigators to request a peer-reviewed publication. Given the extensive time interval between final study end date and publication retrieval, we feel confident that all potential trials were included in this study and we hereby provide an extensive overview of the field. Furthermore, we assessed adherence to both primary and secondary outcomes and further characterize the degree of nonadherence to registered outcomes by independent review of published post hoc outcome measures.

There are some limitations that should be considered when interpreting our findings. First, we found that 20% of all predefined primary outcomes in the trial registrations were not reported in their publications. Given the fact that we found more than 1 publication in 43% of trials, this could indicate duplicate publication by authors, scattering their research results over multiple publications, thereby amplifying their study reach. Because 1 publication per trial was included, we may thus overestimate the proportion of omitted predefined outcome measures. When reviewed within our cohort, however, we did not find a higher incidence of primary or secondary outcome nonadherence in trials with multiple publications. Another noteworthy limitation of this study is the absence of direct inquiries to trial authors regarding justifications for amendments made to the initially registered outcomes after trial initiation or discrepancies between the registered and published outcomes. Future research could further elucidate reasons for outcome reporting bias and enhance awareness of its risks.

In conclusion, we found that trials investigating MS drugs are to a large extent subject to selective outcome reporting, although nonregistered published outcomes were not published in favor of significant positive results. This study highlights the need for rigorous methods to eliminate this type of bias and strengthen future evidence-based medicine within this field.

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Appendix Authors

Name	Location	Contribution
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Suzan van Amerongen, MD	Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands	Major role in the acquisition of data; analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
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Joep Killestein, MD	Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands	Study concept or design; analysis or interpretation of data

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