MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Effect of applying inclusion and exclusion criteria of phase III clinical trials to multiple sclerosis patients in routine clinical care

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Multiple Sclerosis Journal

2021, Vol. 27(12) 1852–1863

DOI: 10.1177/1352458520985118

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Abstract

Background: Newly approved, drug-modifying therapies are associated with still unknown adverse events, although clinical trials leading to approval have strict inclusion and exclusion criteria and analyse safety and efficacy.

Objectives: The aim of this study was to analyse the eligibility of multiple sclerosis (MS) patients treated in routine care into the phase III clinical trial of the respective drug.

Methods: In total, 3577 MS patients with 4312 therapies were analysed. Patients with primary-progressive MS were excluded. Inclusion and exclusion criteria of phase III clinical trials in relapsing–remitting MS were adopted and subsequently applied. A comparison in clinical and sociodemographic characteristics was made between patient who met the criteria and those who did not.

Results: 83% of registered patients would not have been eligible to the respective phase III clinical trial. Relapse was the single most frequent criterion not fulfilled (74.7%), followed by medication history (21.2%).

Conclusion: The majority of MS patients treated in routine care would not have met clinical trials criteria. Thus, the efficacy and safety of therapies in clinical trials can differ from those in the real world. Broader phase III inclusion criteria would increase their eligibility and contribute to a better generalizability of the results in clinical trials.

Keywords: Multiple sclerosis, multiple sclerosis disease therapy, registry, phase III clinical trials, generalizability, drug approval, pharmacoepidemiology, drug safety

Date received: 30 September 2020; revised: 10 December 2020; accepted: 10 December 2020.

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Introduction

Multiple sclerosis (MS) is a neurodegenerative demyelinating and chronic inflammatory disease of the central nervous system that is associated with a variety of symptoms affecting the motor, sensory, visual and autonomic systems.[1] MS shows a broad variability in prevalence across the globe, from high proportions in Europe and North America (>100/100,000 inhabitants) to a low prevalence in Africa and Eastern Asia (2/100,000 inhabitants).[2] The prevalence of MS in Germany is comparable to other European countries and shows a constant increase in the past decades.[3]

The high MS prevalence and the potential severe consequences require appropriate treatments.[4,5] While there is no curative MS treatment, patients are treated with different disease-modifying therapies (DMTs). DMTs show various modes of action, route and frequency of administration, treatment adherence, adverse effects and toxicity.[6] With the approval of interferon beta (IFNβ) and glatiramer acetate for the treatment of relapsing–remitting MS (RRMS), the modern era of MS treatment had started in 1990s. Natalizumab was the first monoclonal antibody used in the MS therapy approved in Germany in 2006. Since then, the development of MS DMTs experienced a strong progress. An important step was the approval of oral medications, first fingolimod, followed by teriflunomide, dimethyl fumarate and cladribine. Ocrelizumab was the first DMT, recently approved for the therapy of primary-progressive MS (PPMS).[7] Siponimod was recently

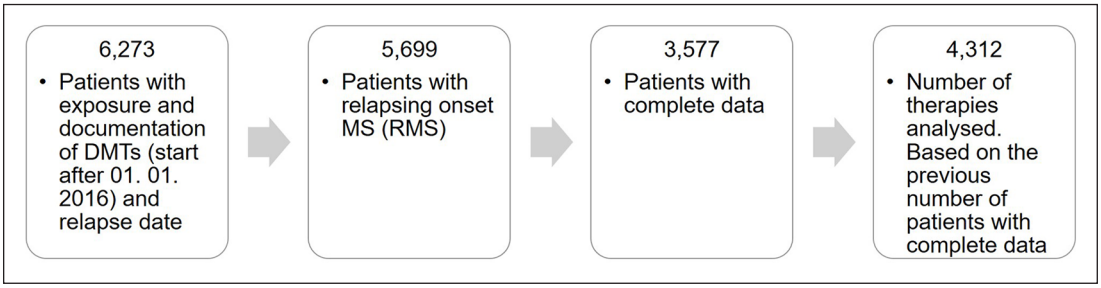

Figure 1. Data flowchart.
DMT: disease-modifying therapies.

approved for the treatment of secondary-progressive MS.

The fast-growing drug market for MS results in many new treatment options and thus includes chances and risks for MS patients. Phase I and II studies are essential parts of clinical drug development. Phase III clinical studies are of crucial importance in drug approval, since they show the efficacy of a drug for patients selected by inclusion and exclusion criteria. In addition, phase III studies provide safety data for many common adverse events.[8] Generalizability describes the transferability of efficacy and safety results from clinical trial patients to patients receiving treatment in clinical routine.[9] Thus, generalizability addresses the effectiveness of a specific intervention in the setting of routine care, sometimes assessed in phase IV studies, post-authorization safety studies (PASS) or registries. These studies enable the assessment of rarer adverse events.

The aim of this study was to evaluate the proportion of MS patients in routine care fulfilling inclusion and exclusion criteria of phase III clinical trials and compare those with and without regarding clinical and sociodemographic characteristics.

Methods

Data source and study population

For this study, data from the German MS Register (GMSR) initiated by the Federal Association of the German Multiple Sclerosis Society (acronym: DMSG) were analysed. The GMSR collects health-related information for MS patients using a web-based documentation system (EDC). Further details of the GMSR have been described elsewhere.[10]

In brief, patients who started a treatment between 1 January 2016 and 31 December 2019 with a DMT (name of the active substance, product name, start date, end date and therapy duration), complete data on gender, age, age at onset, EDSS (expanded disability status scale) score, clinical course and relapse data were analysed. Since exact number of T2 lesions is not collected in GMSR, magnetic resonance imaging (MRI) was not taken into consideration. Initially, 6273 patients with exposure and documentation of selected DMTs were included of which 5699 had a relapsing MS onset. In total, 2122 patients were excluded because of lacking information on clinical data (Figure 1). Although 574 patients with PPMS are in the register, we excluded the PPMS patients due to the small number of patients with full data sets. Exposure with the following DMTs were assessed: ocrelizumab, cladribine, daclizumab, dimethyl fumarate, teriflunomide, alemtuzumab, fingolimod, natalizumab, mitoxantrone, glatiramer acetate, peginterferon β-1a, interferon β-1a and interferon β-1b. Due to the short time on the market, siponimod was not included.

Based on the 'Summary of Product Characteristics' published by the European Medicines Agency and a PubMed literature search for each active substance, reports on phase III clinical trials providing information about clinical efficacy and safety were selected. This included the appendix and protocol as well the ClinicalTrials.gov summary. From these documents, patient in- and exclusion criteria for the respective trial were extracted. Summary of Product Characteristics (SCM) references used in this analysis are listed in the Supplementary File.

Data analysis

In case a patient in the register was treated with several drugs over time, the assessment of in- and exclusion criteria was done for every DMT separately. A patient may thus be included in multiple analyses, for each DMT-treatment with the corresponding data. First, the percentage of patients with eligibility to clinical trial

Table 1. Demographic and clinical characteristics of the GMSR population and analysed patients.

Characteristics	GMSR patients[a]	Analysed patients
No. of patients	5699	3577
No. of DMT,[b] mean (SD)	1.34 (0.74)	1.21 (0.44)
Female (%)	73.30	73.39
Age (years),[c] mean (SD)	40.69 (11.58)	39.68 (11.58)
Age onset (years), mean (SD)	31.322 (10.28)	30.91 (10.16)
DMT duration (days), mean (SD)	541.71 (427.5)	564.31 (390.90)
EDSS score, mean (SD)	2.32 (1.93)	2.06 (1.79)
No. of relapses 12,[d] mean (SD)	0.28 (0.57)	0.31 (0.59)
No. of relapses 24,[e] mean (SD)	0.35 (0.71)	0.40 (0.73)
RRMS (%)	91.55	93.49

GMSR: German multiple sclerosis register; DMT: disease-modifying therapy; EDSS: expanded disability status scale; RRMS: relapsing–remitting multiple sclerosis.
[a]First documented DMT started after 1 January 2016.
[b]Number of DMTs during study period of 1 January 2016 to 31 December 2019 per patient.
[c]At treatment start during study period of 1 January 2016 to 31 December 2019.
[d]Since 2015.
[e]Since 2014.

criteria across different DMTs was described. Next, the proportion of patients fulfilling each criterion of phase III clinical trials for every selected DMT was analysed. Finally, treated patients fulfilling all recruitment inclusion criteria for a specific drug were compared with those who did not with regard to clinical and sociodemographic characteristics.

For continuous variables, between group comparisons were performed using the Student test and for categorical variables the chi-square test. A p value of <0.05 was considered statistically significant. Analyses were performed using STATA/SE 13.0.

Results

Demographic and clinical characteristics

In total, 3577 individual patients with 4312 therapies were analysed (Figure 1). Demographic and clinical characteristics are summarized in Table 1. 73.4% of the patients were female, mean age was 39.7 years (standard deviation (SD) = 11.6) with a range from 14.6 to 76.0 years. The majority (93.5%) suffered from RRMS, 4% from secondary-progressive MS (SPMS) and 2.5% from a clinically isolated syndrome (CIS).

Selection criteria

Table 2 shows a summary of the selected phase III trials for each DMT.[11–30] Age, EDSS score, clinical course and relapses were the most frequent inclusion criteria, whereas medication history was a common exclusion criterion. In most clinical trials, patients were included if they were aged between 18 and 55 years; had a RRMS clinical course with at least two relapses within the last 2 years prior to randomization or one relapse in the year before and/or an MRI scan of the brain showing abnormalities consistent with multiple sclerosis (e. g. at least one gadolinium-enhancing lesion 0–6 weeks to randomization). This inclusion criterion (MRI scan) was not applied due to the limited data. A further selection criterion was an EDSS score between 0.0 and 5.0. A detailed description of the inclusion criteria is shown in Table 3. Table 4 shows the medication history requirements for clinical trial entrance.

Post-approval compliance with selected clinical trial criteria

Across all analysed drugs, 714 (16.56%) treatments were done in patients who would have been included into a phase III clinical trial if all prespecified analysis criteria were applied. If the selection criterion 'relapse' was dropped, 67.5% (2909) would have fulfilled all other prespecified analysis criteria and would therefore been included into the respective phase III clinical trial.

Thus, 'relapse' was the selection criterion with the highest exclusion rate (74.7%) across the different DMTs, followed by 'medication history' (21.2%). 11.8% of the analysed patients did not meet the criterion 'age', while 7.2% of the patients did not conform

Table 2. Summary of phase III clinical trials proving information on safety and efficacy for disease-modifying therapies in multiple sclerosis patients.

Active substance	Name	Pharmacotherapeutic group[a]	EU approval	Trial name	Trial published	Trial reference
Ocrelizumab	Ocrevus	Immunosuppressant	2018	OPERA I and II	2017	11
Cladribine	Mavenclad	Immunosuppressant	2017	CLARITY	2010	12
Daclizumab	Zinbryta	Immunosuppressant	2016	DECIDE	2015	13
				SELECT	2013	14
Dimethyl fumarate	Tecfidera	Antineoplastic and immunomodulating agents	2014	CONFIRM	2012	15
				DEFINE	2012	16
Teriflunomide	Aubagio	Selective immunosuppressant	2013	TOWER	2014	17
				TEMSO	2011	18
Alemtuzumab	Lemtrada	Selective immunosuppressant	2013	CARE MS I	2012	19
				CARE MS II	2012	20
Fingolimod	Gilenya	Immunosuppressant	2011	FREEDOM MS	2010	21
				TRANSFORM	2010	22
Natalizumab	Tysabri	Selective immunosuppressant	2006	AFFIRM	2006	23
Mitoxantrone	Novantrone	Antineoplastic agent	2003	MIMS	2002	24
Glatiramer acetate	Copaxone	Immunostimulants	2001	European/Canadian GA study	2001	25
				Copolymer 1MS study	1995	26
Peginterferon β-1a	Plegridy	Immunostimulants	2014	ADVANCE	2014	27
Interferon β-1a	Rebif	Immunostimulants	1998	STUDY NS26321	1998	28
Interferon β-1a	Avonex	Immunostimulants	1997	PRISM	1995	29
Interferon β-1b	Betaferon	Immunostimulants	1995	IFNB multiple sclerosis study	1993	30

[a]According to Summary of Product Characteristics (SCM) of the European Medicines Agency.

Table 3. Inclusion criteria for phase III clinical trials providing information on clinical efficacy and safety of disease-modifying therapies for multiple sclerosis patients.

DMT	Age	EDSS score	Clinical course	Relapses
Ocrelizumab	18–55	0.0–5.0	RRMS	At least two relapses within the last 2 years prior to screening or one relapse in the year before screening. No relapse 30 days before trial entry
Cladribine	18–65	0.0–5.5	RRMS	At least one relapse within 12 months before study entry. No relapse within 28 days before study entry
Daclizumab	18–55	0.0–5.0	RRMS	At least one relapse in the 12 months before randomization
Dimetyl fumarate	18–55	0.0–5.0	RRMS	At least one relapse within the 12 months before randomization
Teriflunomide	18–55	0.0–5.5	RRMS/SPMS	At least one relapse in the 12 months or at least two relapses in the 24 months before randomization. No relapse within 30 days before randomization
Alemtuzumab	18–55	0.0–5.5	RRMS	At least two relapses in the previous 2 years and at least one in the previous year
Fingolimod	18–55	0.0–5.5	RRMS	At least one relapse during the previous year or at least two relapses during the previous 2 years
Natalizumab	18–50	0.0–5.0	RRMS	At least one relapse within the 12 months before the study began. No relapse within 50 days before the first administration of the study drug
Mitoxantrone	18–55	3.0–6.0	RRMS/SPMS	No relapses 8 weeks before randomization
Glatiramer acetate	18–50	0.0–5.0	RRMS	At least two relapses in the 2 years prior to entry, onset of the first relapse at least 1 year before randomization
Peginterferon β-1a	18–65	0.0–5.0	RRMS	At least two relapses within the last 3 years with at least one occurring in the last 12 months
Interferon β-1a	18–55	0.0–5.0	RRMS	At least two relapses in the previous 2 years
Interferon β-1b	18–55	0.0–5.5	RRMS	At least two relapses in the previous 2 years

DMT: disease-modifying therapy; EDSS score: expanded disability status scale score; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis.

Table 4. Medication history criteria for entrance to a phase III clinical trials providing information on clinical efficacy and safety of disease-modifying therapies for multiple sclerosis patients.

DMT	Medication history
Ocrelizumab	No treatment with β interferons, glatiramer acetate or other immunomodulatory therapies within 4 weeks prior to baseline. No previous treatment with B-cell targeted therapies (rituximab, ocrelizumab) or with alemtuzumab, cladribine, mitoxantrone, daclizumab and teriflunomide. No treatment with cyclophosphamide, azathioprine, methotrexate or natalizumab within 24 months prior to screening. Patients previously treated with natalizumab will be eligible for trial only if duration of treatment was <1 year. No treatment with fingolimod within 24 weeks prior to screening
Cladribine	For patient who had received a DMT, a washout period of at least 3 months before study entry was required. No prior immunosuppressive treatment. No prior natalizumab treatment
Daclizumab	No prior treatment with caldribine. No prior treatment with mitoxantrone, cyclophosphamide, fingolimod or natalizumab within 1 year prior to randomization. No treatment with glatiramer acetate within the 30 days prior to randomization
Dimethyl fumarate	No previous treatment with glatiramer acetate or cladribine. No prior treatment with mitoxantrone within 1 year prior to randomization. No prior treatment with natalizumab within the 6 months prior to randomization. No prior treatment with interferons within the 3 months prior to randomization. No treatment with steroids or oral corticosteroids within 50 days prior to randomization
Teriflunomide	No prior use of glatiramer acetate or interferons in the 3 months prior to randomization. No prior or use of natalizumab, cladribine or mitoxantrone
Alemtuzumab	No treatment within the previous 6 months with natalizumab or methotrexate
Fingolimod	No requirements
Natalizumab	No treatment with mitoxantrone or cyclophosphamide within the previous year. No treatment with interferons, azathioprine, glatiramer acetate or immune globulins within the previous 6 months
Mitoxantrone	No treatment with glucocorticosteroids for at least 8 weeks before baseline. No previous therapy with interferons, glatiramer acetate or mitoxantrone
Glatiramer acetate	No requirements
Peginterferon β-1a	Subjects must have discontinued interferon treatment 6 months prior to baseline. No prior treatment with caldribine, fingolimod or mitoxantrone (1 year prior to baseline) and glatiramer acetate (4 week prior to baseline)
Interferon β-1a	No prior treatment with interferon or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months
Interferon β-1b	No requirements

with the 'EDSS score' criterion. 'Clinical course' (5.4%) leads to the lowest exclusion rate (Figure 2).

Table 5 shows the percentage of patients in this routine care register who would have been selected for a phase III clinical trial of their respective drug. 21.7% of patients treated with alemtuzumab and 20.8% of patients receiving natalizumab fulfilled all five selection criteria, showing the highest concordance with clinical trial criteria, while ocrelizumab (7.6%) and interferon (4.0%) patients had the lowest concordance. 27.7% of fingolimod and 20.22% of glatiramer acetate patients fulfilled all four admission criteria.

When excluding the selection criterion, 'relapse' patients with alemtuzumab (76.5%) and dimethyl fumarate (74.6%) therapy had the highest concordance with the four selection criteria of the respective phase

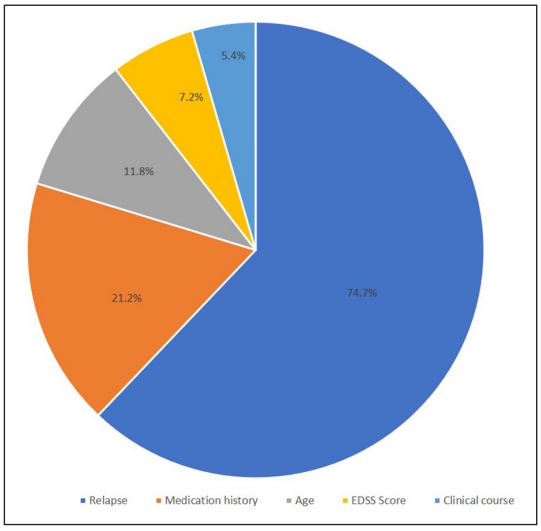

Figure 2. Selected clinical trial criteria and exclusion rates.

Table 5. Percentage of GMSR patients fulfilling phase III clinical trial selection criteria.

DMT	Patients (*N*)	Therapies (*N*)	Percentage of patients fulfilling each criterion					Percentage of patients fulfilling all criteria	Percentage of patients fulfilling four criteria[a]
			Age	EDSS score	Relapse	Clinical course	Medication history		
Ocrelizumab	580	580	85.17	77.07	22.76	86.55	62.76	7.59	39.48
Cladribine	136	136	99.26	90.44	33.82	92.65	50.00	12.50	41.18
Daclizumab	171	171	86.55	84.21	29.24	94.15	81.87	20.47	60.23
Dimethyl fumarate	643	661	92.74	98.18	22.39	96.97	83.96	15.73	74.58
Teriflunomide	521	528	84.66	96.40	20.82	97.73	85.23	14.77	67.61
Alemtuzumab	166	166	96.99	93.37	31.33	99.40	83.73	21.69	76.51
Fingolimod	601	606	89.11	95.21	32.84	97.03	n/a	27.72	84.65
Natalizumab	418	423	88.42	93.38	33.33	97.40	85.34	20.80	68.32
Mitoxantrone	37	37	59.64	62.16	91.89	100.00	94.59	37.84	40.53
Glatiramer acetate	547	554	81.95	98.38	26.53	92.24	n/a	20.22	75.09
Interferons	441	450	92.00	96.89	7.56	93.33	82.89	4.00	69.11

DMT: disease-modifying therapy; EDSS score: expanded disability status scale score.
[a]Percentage of patients fulfilling all criteria when selection criterion relapse was excluded.

III clinical trials, while those treated with cladribine (41.2%) and ocrelizumab (39.5%) showed the lowest.

Comparison of patients treated with DMTs post approval

Table 6 shows the comparison of MS patients with and without fulfillment of the respective phase III criteria. In general, more women than men did not meet the selection criteria. Across all DMTs, with exception of cladribine, patients not fulfilling all criteria were older than patients fulfilling all criteria. With regard to treatment duration, patients on alemtuzumab not fulfilling all inclusion criteria were treated longer (on average 167 days) than those who met all criteria. This difference equals 111 days in patients receiving natalizumab. Statistical significant differences between MS patients with and without fulfillment of the respective phase III criteria are marked in Table 6.

Discussion

In this analysis, we assessed the transferability of clinical trial in- and exclusion criteria to MS patients in routine clinical care using a large MS register in Germany. We showed that the majority of patients treated with DMT in routine care after approval of a DMT would not have met the inclusion criteria for phase III clinical trials leading to approval of the respective drug. This was mainly due one criterion, relapses. Omitting this criterion would increase the proportion of patients fulfilling inclusion criteria to about two-thirds (67.5%).

Phase III clinical trials mainly include patients who experienced at least two relapses in the 2 years prior or at least one relapse during the first year prior to randomization. Since the reduction of the annualized relapse rate (ARR) is a common endpoint in phase-III studies in MS, there is rational for an indication of disease activity. But, not fulfilling this criterion does not imply potential risks since a low relapse rate is an indication for a successful, rather stable disease under current therapy.[31] On the other extreme, patients might receive a DMT too early, inducing potential risks. The omission of the criterion 'relapse' increased the final eligibility for all patients, irrespective of the DMTs, with the exception of mitoxantrone, for which this criterion was defined differently than in other clinical trials. Next to 'relapse', about one in five patients did not fulfill the criterion requirement of 'medication history'. Most of the clinical trials required at least a washout period before randomization; in some trials, a prior DMT therapy acted as an exclusion criterion. Current national guidelines suggest to switch to a second-line therapy if a patient has at least one relapse under DMT or does not respond to the current DMT (e.g. shown by new MRI activity).[32] As a result, most patients receive more than one DMT over the disease course and therefore a treatment history without MS DMT is rare. Furthermore, certain DMTs are known to result in rebound relapses if a treatment is stopped without an appropriate DMT switch.[33] Thus, washout periods as imposed in phase III clinical trials are difficult to achieve in clinical routine. Both might have contributed to the high non-fulfillment of this criterion.

Table 6. Difference (Δ) between patients who would not have been accepted into phase III clinical trial compared patients fulfilling all admission criteria.

Mean Δ	Ocrelizumab	Cladribine	Daclizumab	Dimethyl fumarate	Teriflunomide	Alemtuzumab	Fingolimod	Natalizumab	Mitoxantrone	Glatiramer acetate	Interferons
Patients (therapies)[a]	536 (536)	119 (119)	135 (135)	546 (557)	447 (450)	130 (130)	437 (438)	331 (335)	23 (23)	436 (442)	425 (432)
Female (%)	0.63**	5.04	4.39	−0.20	5.85	−5.18	5.57	4,05	−1.86	−0.53*	12.5
Age (years)	3.98*	−6.47*	6.59**	2.38*	3.61**	3.21	3.66***	1.93	11.29***	3.21***	2.48
Age onset (years)	0.68	−3.63	1.95	0.54	1.77	3.47*	1.79	1.23	7.44*	4.22***	2.78
DMT duration (days)	40.10	74.39	−4.91	10.79	−16.62	167.89*	98.25**	111.18*	−68.35	−60.09	66.26
DMTs, No	−0.23	−0.07	0.51	−0.05	0.04	−0.20**	−0.22***	−0.18*	−0.35	0.07	−0.09
EDSS score	0.79*	−0.56	1.11**	0	0.51**	0	0.30	0 .36	0.84	0.13	0.37
Relapses 12, No.	−0.89***	−1.06***	−1.19***	−1.17***	−1.05***	−1.37***	−1.22***	−1.14***	0.36***	−1.13***	−1.54***
Relapses 24, No.	−0.99***	−1.17***	−1.29***	1.28***	−1.10***	−1.52***	−1.54***	−1.29***	0.44***	−1.21***	−1.76***

DMT: disease-modifying therapy; EDSS: expanded disability status scale; No.: number.
[a]Number of patients (therapies) missed at least one selection criterion; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Several studies investigated clinical trial generalizability in different disease indications, for instance, cardiovascular diseases, cancer and lung diseases. According to the review of He et al.,[9] who assessed generalizability of clinical trials in the big data era, 59.9% (111) of the published studies concluded that the evaluated trials are not generalizable, whereas 29.4% concluded that they are. 11.2% (21) of authors reported mixed results. This study for MS patients is in concordance with similar studies in other disease. No generalizability studies of clinical trials for DMTs in MS have been published yet.

The severity of disease, pharmacological response and adverse events show a decent variability in different patient populations. Children, elderly, both men and women as well as individuals with different genotypes show divergent pharmacokinetic and pharmacodynamic profiles.[34] Thus, therapy should be adapted especially in term of dose adjustment and safety. Most phase III clinical trials exclude patients younger than 18 and older than 55 years. Thus, post-approval studies providing information on clinical safety and efficacy in these population groups are rare. Consequently, potential risks for drug safety in these groups are less known. But different characteristics of patients who do not fulfill inclusion criteria will have different importance when inferences on effects and risks of a new drug are made to those not included in the clinical trial. Patients not fulfilling all criteria in our register were on average older than those fulfilling all inclusion criteria. Similarly, in the groups with at least one selection criterion, missing women were more often included than men, indicating a limitation of gender generalizability.

Our study has several limitations. Several patients were excluded because of incomplete documentation, resulting in a smaller sample size for some DMTs which could imply a generalizability issue for those DMTs. Some of the phase III clinical trials applied MRI of the brain indicating MS comparable abnormalities (e. g. at least one gadolinium-enhancing lesion 0–6 weeks to randomization) as an inclusion criterion. Because of incomplete MRI data, this criterion was not applied to the GMSR patients, a further limitation of our study. However, this mirrors the real world, since MRIs are not standardized and can only be compared to a trial situation to a limited extent because different images are evaluated by different radiologists.[35] An additional limitation is the lack of treatment-related outcomes (e.g. adverse events) in the register. Thus, we could not investigate differences in outcomes between patient who met the criteria and those who did not.

In conclusion, we found that the majority of MS patients treated with a DMT in routine care would not have been included into the clinical trial that led to the approval of the respective drug. Regulatory agencies and clinical trial investigators may change the approach in trial design in order to ensure a more representative patient population enrolment. By contrast, more heterogeneous trials with lower probability of an endpoint occurrence may require larger sample sizes increasing the costs of trials and decelerate the progression of drug development due to recruitment concerns.

A priori generalizability studies based on registry data and trial design information might be a chance for investigators to adapt studies before start. Posteriori generalizability studies, like the present one, may benefit from data linkage, bringing together primary registry and secondary data (for instance, data from health insurances) in order to describe the clinical care routine and the treated population even better. An integration of a priori generalizability studies, a posteriori generalizability studies, and randomized clinical trials would result in an improvement in the drug life cycle in consideration for a safe and efficient drug therapy. Another approach in the implementation of clinical trials in clinical care routine could be the establishment of registry-based randomized clinical trials.

Acknowledgements

The authors would like to thank all patients who have given their informed consent to be included in GMSR. Furthermore, this study would not have been possible without the efforts of the centres participating in the registries. They thank all members of staff in all contributing centres for their continued efforts. Centres that provided data for this study are listed below. Medizinische Versorgungszentren, Altenburger Land GmbH, Altenburg. Gemeinschaftspraxis Dr. med. A. Safavi and M. Schädel, Alzenau. Neurozentrum Alzey, Dr. Loos/Dr. Bernhard, Alzey. Rhein-Mosel-Fachklinik Andernach, Zentrum für Psychiatrie, Psychotherapie und Neurologie, Andernach. DRK Kamillus Klinik, Neurologische Abteilung, Asbach. Praxis Dr. Hofmann, Aschaffenburg. Zentrum für Neurologie, Psychiatrie und Psychotherapie Asperg, Asperg. HELIOS Klinikum Aue, Klinik für Neurologie, Aue. Universitätsklinikum Augsburg, Neurologische Klinik mit klinischer Neurophysiologie, Augsburg. Dr. Schöll, Dr. Steidl & Kollegen, Bad Homburg. Caritas-Krankenhaus Bad Mergentheim gGmbH, Klinik für Neurologie, Bad Mergentheim. Rhön-Klinikum Campus Bad Neustadt, Klinik für Neurologie, Bad Neustadt a. d. Saale. Johanniter Ordenshäuser, Neurologische Abteilung, Bad Oeynhausen. MediClin Reha-Zentrum Bad Orb, Neuro-orthopädisches Reha-Zentrum, Bad Orb. Agaplesion Ev. Bathildis Krankenhaus, Neurologische Ambulanz, Bad Pyrmont. Segeberger Kliniken GmbH, Neurologisches Zentrum, Bad Segeberg. Neurologisches Rehabilitationszentrum Quellenhof, Bad Wildbad. Wicker-Klinik, Neurologische Abteilung, Bad Wildungen. Dr. Becker Kiliani-Klinik, Neurologische Abteilung, Bad Windsheim. Hardtwaldklinik I, Neurologisches Zentrum, Werner Wicker GmbH & Co. KG, Bad Zwesten. Neurologische Klinik Selzer GmbH, Baiersbronn. Kallmann Neurologie–Multiple Sklerose Zentrum Bamberg (MSZB), Dr. med. Boris-A. Kallmann, Bamberg. Praxisklinik für Neurologie, Psychiatrie, Psychosomatische Medizin und Psychotherapie, Dres. Käfferlein, Dengler, Jung und Schreiber, Bamberg. Klinik Hohe Warte Bayreuth, Neurologische Klinik, Bayreuth. Marianne-Strauß-Klinik, Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke gemeinnützige GmbH, Berg. Charité–Universitätsmedizin Berlin, Ambulanz für Multiple Sklerose und Neuroimmunologie, Berlin. Alexianer St. Joseph-Krankenhaus Berlin-Weißensee, Klinik für Neurologie/MS-Ambulanz §116 B, Berlin. Jüdisches Krankenhaus Berlin, Akademisches Lehrkrankenhaus der Charite, Zentrum für Multiple Sklerose, Berlin. Vivantes Klinikum Neukölln–Klinik für Neurologie, Spezialambulanz für Multiple Sklerose, Berlin. Neurologische Praxis, MD Turki Akil, Berlin. Evangelisches Krankenhaus Bethel gGmbH, Klinik für Neurologie, Bielefeld. Neurozentrum Bielefeld-Brackwede, Dres. med. J. und M. Böhringer, Dr. J. Katzmann, F. Sudfeldt, Bielefeld. Medical Park Loipl, Bischofswiesen. Neurologische Praxis, Böblingen. Gemeinschaftspraxis Dres. med. Niederhofer, Kauermann, Küper, Bochum. Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil gGmbH, Neurologische Klinik und Poliklinik, Bochum. St. Josef-Hospital, Klinikum der Ruhr-Universität Bochum, Klinik für Neurologie, Bochum. Neurologische Facharztpraxis Dr. I. Nastos, Bochum. Gemeinschaftspraxis Kausch & Lippert, Bogen. Neurologische Gemeinschaftspraxis, Bonn. Neurologisches Rehabilitationszentrum Godeshöhe e.V., Bonn. Asklepios Fachklinikum Brandenburg, Klinik für Neurologie, Brandenburg. Neurozentrum Schlosscarree, Dr. med. Ekkehard Klippel, Braunschweig. Neurologie am Ziegenmarkt, Braunschweig. Städtisches Klinikum Braunschweig gGmbH, Neurologische Klinik, Braunschweig. Klinikum Bremerhaven Reinkenheide, Neurologische Tagesklinik, Bremerhaven. Carl-Thiem Klinikum

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Praxis rechts vom Rhein, Dr. med. Jan-Dirk Seifert und PD Dr. med. Hela-Felicitas Petereit, Köln. NeuroMed Campus Nelles, Scharpegge, Haupt, Scharwat, Fachärzte für Neurologie, Schmerztherapie, Köln. Universitätsklinikum Köln, Klinik und Poliklinik für Neurologie, Köln. Kliniken Schmieder Konstanz, Neurologisches Fach- und Rehabilitationskrankenhaus, Konstanz. Facharztpraxis für Neurologie und Psychiatrie, im Facharztzentrum am Klinikum Konstanz, Konstanz. Praxisgemeinschaft Neurologie am Zoo, Krefeld. Gemeinschaftspraxis Dr. med. B. Wittmann & P. Rieger, Landshut. Praxis Dr. Pfeffer & Dr. Staudinger-Pfeffer, Praxis für Neurologie und Psychiatrie, Landshut. Ärztehaus Stötteritz, Neurologische Praxis, Leipzig. hygieia.net Leipzig, Leipzig. Klinikum Lippe-Lemgo, Neurologische Klinik, Lemgo. Helios Klinik Lengerich GmbH, Abteilung Neurologie, Lengerich. Märkische Kliniken GmbH, Klinikum Lüdenscheid, Klinik für Neurologie, Lüdenscheid. 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Gemeinschaftspraxis Dres. Uhlig/Windsheimer, Nürnberg. Praxis Dres. Schlüter, Beckmann, Berufsausübungsgemeinschaft, Öhringen. Neurologie an der Hase, Holger Lorenzen, Dr. med. Edzard Ites, Stephan Ulf Sylvester, Jens Gläscher, Dr. med. Elisabeth Rehkopf, Osnabrück. MVZ für Neurologie der Paracelsus-Klinik Osnabrück, Osnabrück. Praxis Dr. med. Christoph Schenk, Osnabrück. Klinikum Osnabrück GmbH, Neurologische Klinik, Osnabrück. Praxis Dr. Roth & Partner, Facharzt für Nervenheilkunde, Ostfildern. St. Vincenz-Krankenhaus GmbH Paderborn, Neurologische Klinik, Paderborn. Neurozentrum Peine, Peine. Facharztpraxis für Neurologie und Psychiatrie, Andreas Stockert und Dr. Claudia Rettenmayr, Pforzheim. St. Josefs-Krankenhaus Potsdam, Klinik für Neurologie, Potsdam. Praxis Dr. Altmann, Facharzt für Neurologie und Psychiatrie, Potsdam. VAMED Klinik Schloss Pulsnitz GmbH, Pulsnitz. Neurozentrum Ravensburg, Dres. Dieterle/Kunz, Ravensburg. 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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: The German MS Registry of the German MS Society was initiated and funded by the German MS Foundation and the German MS Society in 2001. The foundation and the society kept funding the operation since. It is operated by a non-profit company, the MSFP. In 2018, the MSFP received a grant from Merck and Novartis to support the extension of the registry and implementation of EMA requirements. In 2019, Biogen and Celgene joined the multi-stakeholder funding approach to support the registry's operation and to allow the collection and reporting of data required as part of the EMA-minimal data set. Industry funding does not result in restriction to publish data, nor do the funders have access to raw data or influence in the scientific conduct of the registry. K.O.J. has nothing to disclose. D.E. has nothing to disclose. P.R. has received honoraria for lectures or consultancy from AbbVie, Alexion, Almirall, Biogen, Merck, Novartis, Sandoz, Sanofi Genzyme, Roche and Teva. He received research grants from Amicus, Biogen, Merck and Roche. A.S. has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives funding from a range of public and corporate sponsors, recently including The German Innovation Fund (GBA), The German MS Trust, Biogen, German MS Society, Celgene (BMS), Merck and Novartis. U.Z. has received speaker fees, travel compensation and/or his section received research support from Alexion, Almirall, Bayer Health Care, Biogen, Celgene, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, Teva and grants from German Ministry for Education and Research (BMBF), German Ministry for Economy (BMWi), Deutsche Forschungsgemeinschaft (DFG), European Union (EU), outside the submitted work. K.B. has received funding from the German Ministry of Education and Research, for a project within the Competence Net Multiple Sclerosis and from the German Innovation Fund (GBA) for the coordination of the VersiMs project (both to the University of Münster).

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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