Real-World Evidence on the Societal Economic Relapse Costs in Patients with Multiple Sclerosis

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Abstract

Background Relapses are the hallmark of multiple sclerosis (MS). Analyses have shown that the cost of MS increases during periods of relapse. However, results are inconsistent between studies, possibly due to different study designs and the different implications of relapses with respect to patient characteristics.

Objectives The aims were to estimate and describe direct and indirect relapse costs and to determine differences in costs with respect to patient characteristics. Furthermore, we describe the pharmacoeconomic impact during the relapse follow-up.

Methods Data were extracted from two German, multicenter, observational studies applying a validated resource costs instrument. Relapse costs were calculated as the difference in quarterly costs between propensity score (PS)–matched patients with and without relapses (1:1 ratio). For relapse active patients, we additionally calculated the difference between quarterly costs prior to and during relapse and determined costs in the post-relapse quarter.

Results Of 1882 patients, 607 (32%) presented at least one relapse. After PS-matching, 597 relapse active and relapse inactive patients were retained. Relapse costs (in 2019 values) ranged between €791 (age 50+ years) and €1910 (disease duration <5 years). In mildly disabled and recently diagnosed patients, indirect relapse costs (range €1073–€1207) constantly outweighed direct costs (range €591–€703). The increase from prior quarter to relapse quarter was strongest for inpatient stays (+366%, €432; $p < 0.001$), day admissions (+228%, €57; $p < 0.001$), and absenteeism (127%, €463; $p < 0.001$). In the post-relapse quarter, direct costs and costs of absenteeism remained elevated for patients with relapse-associated worsening.

Conclusion A recent diagnosis and mild disability lead to high relapse costs. The results suggest the necessity to incorporate patient characteristics when assessing relapse costs.

1 Introduction

Relapsing remitting multiple sclerosis (MS) is a chronic disease of the central nervous system with an unpredictable course and relapses as a hallmark. Clinically, a relapse is defined as a worsening or appearance of new neurological symptoms in the absence of fever or infection lasting more than 24 h followed by a period of partial or complete recovery [1, 2]. However, it

has been reported that 57% of relapse deficits do not recover completely and neurological deficits remain, contributing to so called relapse-associated worsening (RAW) [3].

From the patient's perspective, relapses are associated with sudden considerable impairments in health-related quality of life and substantial functional and mental impairments [4]. From a societal perspective, relapses lead to immense economic costs due to increased utilization of direct and indirect resources [5–9]. The intensity of a relapse determines the costs of managing relapse symptoms [10–12]. During relapse periods, increases in direct costs are driven by inpatient stays, medications, and ambulatory care, while indirect economic burden increases due to restrictions in work performance [10, 13].

A recent study estimated the mean societal costs of a relapse at €2468 (in 2015 values) for Germany, and costs ranged between €632 and €4569 (both in 2015 values) in 15 other European countries [6, 14]. These studies calculated relapse costs as the difference between the costs of patients with and without relapses, but did not consider

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Key Points for Decision Makers

For the case of multiple sclerosis (MS), relapses increased the societal economic burden by €1388 on average, but costs varied substantially within patients, between €791 (age 50+) and €1910 (disease duration < 5 years).

In patients with relapse-associated worsening, relapse-associated resource costs remain elevated in the post-relapse period, indicating the need for treatment of residual disability.

Future health economic assessments might incorporate patients' disease characteristics to appropriately assess relapse costs.

any subgroups [6, 14]. However, differences in relapse costs between subgroups are likely since relapses and the associated costs might vary across and within individuals with respect to disease severity, disease duration, gender, or therapy [5, 15, 16]. The main objectives of our analyses were to estimate and describe relapse costs and to determine whether and how relapse costs differ with respect to disease and patient characteristics, using real-world evidence from Germany. Furthermore, we described the pharmacoeconomic impact during the relapse follow-up.

2 Methods

2.1 Study Design, Population, and Ethics

Two-year clinical and health resource utilization data on relapsing–remitting multiple sclerosis (RRMS) patients were extracted from two prospective, non-interventional, multicenter studies with observational periods ending in 2015 (PANGAEA) and 2013 (PEARL). Study design as well as inclusion criteria have been described in detail previously [17, 18]. The studies included patients either treated with beta-interferons or glatiramer acetate (PEARL) or fingolimod (PANGAEA), and no exclusion criteria except for the contraindications mentioned in the respective summary of the product information were applied. In both studies, health economic and clinical data were collected with equal regularity per quarter. Approval for both studies was obtained from independent, local competent ethics committees, and all patients provided written informed consent for the collection of clinical and health economic information. The current analyses were limited to patients with a baseline Expanded Disability Status Scale (EDSS) score lower than 6.0 to ensure a sufficiently large population in each EDSS

step. Furthermore, we excluded 77 persons who had fewer than three visits. The excluded persons did not statistically significantly differ in their sociodemographic or disease characteristics.

2.2 Economic and Clinical Outcomes

The Multiple Sclerosis-Health Resource Survey (MS-HRS) was used in the PEARL and PANGAEA studies to holistically quantify and value resources using the most accurate form of bottom-up microcosting. We chose a societal perspective in which all resources are considered regardless of who bears them [19, 20]. Costs were categorized into direct medical (inpatient stays, day admissions, physician consultations, examinations, over-the-counter [OTC] medication, medical consumables, and professional care), direct non-medical costs (informal care, investments/purchases), and indirect costs. Within indirect costs, we considered absenteeism, either short term (sick leave) or long term (disability pension), but also presenteeism, which refers to impaired performance during work.

Resources were valued at the societal opportunity cost or the best possible approximation using official statistics and administrative data [19, 21]. Valuations of direct medical resources were taken from Bock et al. [21]. To value direct non-medical informal care, we used the opportunity cost method. The informal caregiver's forgone benefits are approximated by multiplying the hours spent on informal care by the opportunity costs of leisure time (€23.30/h) [21, 22]. Indirect costs were valued using the human capital approach. For short-term absence (sick leave), we multiplied the hours of absence from work with the average labor costs in Germany (€33.04/h). For long-term absence (disability pension), we multiplied the average daily labor costs (€199.40/day) with the average number of working days (233 days) and the disability percentage (0–100%), leading to a maximum amount of €46,460.14 per year. Quarterly costs due to presenteeism were calculated by multiplying the quarterly average percentage of reduction in productivity with the quarterly labor costs. A list of all considered resources and their valuation is publicly accessible in Ness et al. [19]. Costs are reported per quarter according to the recall periods in the MS-HRS and are presented in 2019 Euros [19]. Adjustments for inflation were performed using the harmonized consumer price index published by the Federal Statistical Office as recommended for Germany [23, 24].

Relapses and EDSS were assessed every 3 and 6 months, respectively, according to the clinical judgment of physicians during routine clinical visits. RAW was defined as a relapse with incomplete recovery resulting in an increase in EDSS of ≥ 1.5 points, ≥ 1 point, or ≥ 0.5 points for a reference score of 0, 1.0–5.0, or ≥ 5.5 , respectively, with confirmation after ≥ 6 months. Due to its higher sensitivity, we

implemented a roving EDSS reference, so that the obtained EDSS increase is compared with the last EDSS assessment instead of the baseline score [25, 26].

Additionally, we reported costs stratified by body mass index (BMI). Therefore, we examined the weight and height of the patients and classified them as under- or normal weight ($< 25 \text{ kg/m}^2$), overweight, including pre-obesity ($25\text{--}30 \text{ kg/m}^2$), and obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) [27].

2.3 Data Processing

Patients were considered as ‘relapse active’ if they had at least one relapse during the 2-year follow-up, whereas ‘relapse inactive’ refers to patients without relapses during the follow-up time. We calculated relapse costs as the cross-sectional difference in the mean quarterly costs between relapse active patients during relapse quarters and relapse inactive patients. For the relapse costs analysis, we applied propensity score (PS) matching to compensate for differences between relapse active and relapse inactive patients. Patients were matched in a 1:1 ratio using nearest-neighbor matching. PSs were calculated as the probability to be part of the relapse active group according to the following baseline predictors: EDSS score, time since diagnosis of MS, disease-modifying therapies (DMTs), age, and gender. These variables were selected for matching as previous studies showed that a shorter disease duration and lower EDSS are associated with higher relapse activity and that women tend to experience more relapses [28]. Furthermore, DMTs are associated with varying effectiveness in reducing relapse rates [29]. More detailed information on the PS matching can be found in Supplement 1 and Supplement 2 in the electronic supplementary material. In addition to the cross-sectional approach of calculating relapse costs, we analyzed relapse-associated costs longitudinally. Each relapse quarter was re-baselined, and costs for corresponding intervals before (prior relapse) and after this interval (post relapse) were calculated additionally. On an intraindividual basis, we calculated the difference between quarterly costs prior to relapse and quarterly cost during relapse.

2.4 Statistical Analysis

All analyses were descriptive in nature. Frequency counts (n) and proportions (%) were used to summarize categorical variables. Means and standard deviations ($\pm \text{SD}$) were used as appropriate for continuous variables. Statistical differences between patient characteristics were analyzed using Chi-squared and Mann–Whitney U tests. P values for differences in relapse costs between patient and disease strata were derived from generalized linear models with a negative binomial distribution and the respective cost category as the dependent variable. The models included the characteristic

(gender, age, BMI, disease duration, EDSS, or therapy) of interest as well as a variable indicating the relapse status (relapse active vs relapse inactive) and the interaction of both (Supplement 3; see the electronic supplementary material). For example, to assess statistical differences in total relapse costs regarding disease duration, we included the disease duration variable, the variable indicating the relapse status, and the interaction of these two variables as independent variables. All reported p values were compared to an alpha-error level of 5%. Statistical analyses were performed using SPSS statistics for Windows version 25 and PS matching was performed using the MatchIt package (version 3.0.2) in R (version 3.5.1).

3 Results

3.1 Patient Characteristics

Out of 1959 principal eligible subjects, we excluded 77 persons who had less than three visits, so that 1882 patients were included in the analysis. Of these, 607 (32%) presented at least one relapse, while 1275 patients (68%) were free of relapse activity during the 2-year study period (Table 1). Compared with relapse inactive patients, relapse active patients were younger (40.46 ± 9.98 years of age vs 42.09 ± 10.01 years of age, $p < 0.01$), more often female (76% vs 70%, $p < 0.01$), more severely disabled (2.41 ± 1.30 EDSS and 2.17 ± 1.39 EDSS, $p < 0.001$), and more often employed (64% vs 62%, $p = 0.712$). The cohorts did not differ in BMI, with average scores of 25.45 ± 5.14 and 25.66 ± 5.11 for the relapse inactive and relapse active populations, respectively. After PS matching, 597 out of 607 patients per cohort were retained for further analysis. The PS matching resulted in an alignment of the relapse inactive and relapse active populations (Supplement 1; see the electronic supplementary material). There were no statistically significant differences between the matched cohorts (Table 1). One quarter (25%) of the relapse active patients presented with RAW.

3.2 Comparison of Total Relapse Costs

The relapse active cohort incurred significantly higher costs during relapses compared to the relapse inactive cohort ($p < 0.001$) (Fig. 1). More specifically, total relapse costs amounted to €1388, consisting of €618 (45%) direct and €770 (55%) indirect costs. Differences in direct costs arose essentially from inpatient treatment (relapse inactive €103 vs relapse active €550), day admissions (relapse inactive €10 vs relapse active €82), and physician consultations (relapse inactive €168 vs relapse active €257), while costs

Table 1 Characteristics in patients with and without relapses during follow-up

	Unmatched population			Matched set		
	Relapse inactive (<i>n</i> = 1275)	Relapse active (<i>n</i> = 607)	<i>P</i> value	Relapse inactive (<i>n</i> = 597)	Relapse active (<i>n</i> = 597)	<i>P</i> value
Socio-demographic characteristics						
Female gender, <i>n</i> (%)	896 (70)	464 (76)	0.006 ^a	459 (77)	454 (76)	0.733 ^a
Age, years, mean (SD)	42.09 (10.01)	40.46 (9.98)	0.002 ^b	41.14 (9.74)	40.68 (9.85)	0.431 ^b
18–39 years, <i>n</i> (%)	492 (39)	266 (44)		248 (42)	257 (43)	
40–49 years, <i>n</i> (%)	464 (36)	225 (37)		215 (36)	224 (38)	
50 years and older, <i>n</i> (%)	319 (25)	116 (19)		134 (22)	116 (19)	
BMI, mean (SD)	25.45 (5.14)	25.66 (5.11)	0.239 ^b	25.23 (5.02)	25.11 (4.97)	0.050 ^b
Under-/normal weight (BMI < 25), <i>n</i> (%)	687 (56)	340 (58)		312 (54)	335 (58)	
Overweight (BMI 25–<30), <i>n</i> (%)	334 (27)	159 (27)		164 (29)	157 (27)	
Obese (BMI 30+), <i>n</i> (%)	202 (17)	92 (16)		99 (17)	89 (15)	
Disease characteristics						
Disease duration, mean (SD)	7.53 (6.16)	6.78 (5.47)	0.027 ^b	6.82 (5.60)	6.83 (5.47)	0.957 ^b
EDSS, mean (SD); median	2.17 (1.39); 2	2.41 (1.30); 2	0.000 ^b	2.33 (1.31); 2	2.40 (1.31); 2	0.503 ^b
0–1.5, <i>n</i> (%)	519 (41)	185 (30)		179 (30)	185 (31)	
2.0–3.5, <i>n</i> (%)	535 (42)	320 (53)		316 (53)	312 (52)	
4–5.5, <i>n</i> (%)	221 (17)	102 (17)		102 (17)	100 (17)	
Relapse-associated worsening			< 0.001 ^a			< 0.001 ^a
No, <i>n</i> (%)	1275 (100)	457 (75)		597 (100)	448 (75)	
Yes, <i>n</i> (%)	0 (0)	150 (25)		0 (0)	149 (25)	
Therapy			0.003			0.77
BRACE, <i>n</i> (%)	958 (75)	493 (81)		479 (80)	483 (81)	
Fingolimod, <i>n</i> (%)	317 (25)	114 (19)		118 (20)	114 (19)	

BMI body mass index, BRACE beta-interferons and glatiramer acetate, EDSS Expanded Disability Status Scale, SD standard deviation

^aChi-Squared

^bMann–Whitney *U*

of absenteeism (relapse inactive €152 vs relapse active €820) were mainly responsible for indirect relapse costs.

3.3 Relapse Costs Stratified by Patient and Disease Characteristics

There were noticeable patterns in relapse costs regarding disease and patient characteristics (Table 2). Total relapse costs were higher in patients with shorter disease duration (< 5 years €1910 vs > 10 years €853; $p < 0.001$) and those being mildly disabled (EDSS 0–1.5 €1664 vs EDSS 4.5–5.5 €1071; $p < 0.001$). In mildly disabled patients and those with a short disease duration, indirect relapse costs (range €1073–€1207) constantly outweighed direct costs (€591–€703). Men incurred higher total relapse costs compared to women (€1603 vs €1322), which is mostly due to higher indirect work-related relapse costs (€1016 vs €694). However, differences were not statistically significant. Furthermore, patients on fingolimod incurred lower relapse costs throughout all cost categories compared to patients on

beta-interferons and glatiramer acetate (BRACE) therapy (total relapse costs €1179 vs €1436), with noticeable differences in direct relapse costs (€350 vs €679). A detailed breakdown of these costs is provided in Supplement 4 (see the electronic supplementary material).

A higher economic burden for patients with short disease duration and those that are mildly disabled was also observed when assessing the increase in resource costs from prior relapse to relapse quarter in relapse active patients. However, relapse-associated costs were lower throughout all subgroups in this predisposed relapse active only population.

3.4 Longitudinal Intraindividual Relapse-Associated Costs

In the relapse active cohort, costs increased significantly from prior relapse to the relapse period (total €1148; $p < 0.001$). In detail, direct and indirect costs increased by €579 ($p < 0.001$) and €569 ($p < 0.001$), respectively. The increase was strongest for inpatient stays (+366%, €432;

Fig. 1 Resource costs (3 months) for relapse inactive ($n=597$) and relapse active (RAW $n=149$; not RAW $n=448$) patients (before, during, and after relapse). Relapse costs, defined as the difference in inactive and active patients during relapses, were significant (Δ

€1388, $p < 0.001$). A significant increase was also observed between prior relapse and during relapse quarters *Prior relapse* 3 months before relapse quarter, *during relapse* relapse quarter, *post relapse* 3 months after relapse quarter. RAW relapse-associated worsening

$p < 0.001$) and day admissions (+228%, €57; $p < 0.001$) in direct costs, while in indirect costs, the increase was higher in costs of absenteeism (127%, €463; $p < 0.001$) than in those of presenteeism (11%, €98; $p = 0.002$). Costs mostly decreased in the post-relapse quarter close to the initial level. However, in patients with RAW, direct costs and costs of absenteeism remained elevated (Fig. 2).

4 Discussion

Our analysis revealed new detailed insights on the societal economic costs of MS relapses. We showed a great variability in societal economic costs associated with relapses. More precisely, patients with less severe burden of disease (young, mild to moderate disabled, short disease duration) are more likely to incur higher relapse costs. In these patients, indirect work-related costs accounted for the majority of costs. Furthermore, we confirmed that relapse costs arise essentially from inpatient stays and absenteeism. In future economic evaluations in MS, the accuracy of relapse costs can be improved if patient and disease characteristics are taken into account.

The study population corresponded in its patient characteristics to a typical clinical RRMS population. Nearly two thirds of the population were female, mild to moderately affected, reported an average age of about 41 years, and a mean disease duration of 7 years. Data were obtained

from multiple study centers across Germany. A real-world setting was further supported by the fact that no explicit exclusion criteria were applied except contraindications associated with current DMTs. Additionally, our estimates are based on a validated health resource survey and applied quarterly in a clinical practice setting to generate robust cost estimates. The results of this analysis are expected to be largely transferable to a broader MS population in Germany. However, caution is needed when transferring the results to other countries due to different healthcare system structures.

Relapse costs have been investigated repeatedly in cross-sectional studies, with highly variable methodologies and results ranging from €503 to €8862 [10, 14]. Most commonly, relapse costs were calculated as the difference between costs of patients with and without relapses without presenting characteristics of these distinct populations [5, 14]. Less frequently, relapse-associated costs were directly enquired in interviews [10]. This methodology can be critically questioned because patients are required to differentiate between routinely utilized resources and relapse-related resources. We extended the first mentioned approach by applying PS matching. Each relapse active patient was assigned to a statistical twin which was relapse inactive. We reported relapse costs stratified by patient and disease characteristics, with estimated relapse costs ranging between €791 (age 50+ years) and €1910 (disease duration < 5 years). The matched and unmatched total relapse cost estimates differed by up to 23% due to the heterogeneity in patient

Table 2 Total, direct, and indirect relapse costs (Δ) stratified by patient and disease characteristics

	Total mean quarterly costs in Euro (SD)		Direct mean quarterly costs in Euro (SD)		Indirect mean quarterly costs in Euro (SD)	
	Cost without relapse	Relapse costs (Δ)	Cost without relapse	Relapse costs (Δ)	Cost without relapse	Relapse costs (Δ)
Gender						
Male (a)	2214 (2226)	1603	344 (523)	587	1870 (2097)	1016
Female (b)	2297 (2548)	1322	380 (779)	628	1917 (2280)	694
Age						
18–39 (c)	1619 (2038)	1552 ^e	254 (478)	758 ^{d,e}	1365 (1886)	794
40–49 (d)	2562 (2517)	1580	468 (779)	550 ^c	2094 (2270)	1030
50+ (e)	3040 (2836)	791 ^c	434 (963)	451 ^c	2605 (2537)	340
BMI						
<25 (f)	2078 (2446)	1137	352 (818)	514	1726 (2169)	623
25–30 (g)	2536 (2493)	1680	394 (652)	807	2142 (2305)	872
>30 (h)	2568 (2520)	1826	426 (574)	647	2141 (2341)	1179
Disease duration						
<5 years (i)	1722 (2065)	1910 ^{j,k}	329 (574)	703	1393 (1889)	1207 ^{j,k}
5–10 years (j)	2691 (2610)	788 ⁱ	413 (759)	511	2278 (2364)	277 ⁱ
>10 years (k)	3089 (2865)	853 ⁱ	423 (971)	546	2666 (2529)	307 ⁱ
EDSS						
0–1.5 (l)	890 (1330)	1664 ^{m,n}	151 (219)	591	739 (1257)	1073 ^{m,n}
2–3.5 (m)	2540 (2326)	1381 ^l	394 (606)	638	2147 (2175)	743 ^l
4–5.5 (n)	3899 (3148)	1071 ^l	690 (1305)	637	3208 (2773)	434 ^l
Therapy						
BRACE (o)	2263 (2473)	1436	358 (704)	679	1905 (2260)	757
Fingolimod (p)	2336 (2500)	1179	427 (816)	350	1909 (2151)	830

Relapse costs were defined as the difference in quarterly costs (Δ) between relapse inactive patients and relapse active patients during relapse quarters. *P* values were derived from generalized linear models using the respective cost category as the outcome. The models included the respective characteristic (gender, age, BMI, disease duration, EDSS, or therapy) as well as a variable indicating the relapse status and the interaction of both. Exact *p* values are reported in Supplement 3

Superscripted letters indicate statistical differences ($p < 0.05$) between the marked group (Δ column) and the group represented by the letter (*first column*). For example, patients with a disease duration of <5 years (i) had significantly higher total relapse costs compared to patients with disease durations between 5 and 10 years (j) and >10 years (k)

BMI body mass index, *BRACE* beta-interferons and glatiramer acetate, *EDSS* Expanded Disability Status Scale, *SD* standard deviation

and disease characteristics in the respective populations (Supplement 5; see the electronic supplementary material). The wide range of relapse costs in the PS-matched analysis suggests that the precision of cost estimates will increase if patient and disease characteristics are taken into account.

Former studies hypothesized that relapses may have a stronger effect in patients with limited permanent disability; however, a systematic investigation of this hypothesis remains unfulfilled [30]. With regard to our analysis, we can confirm that patients with a less severe burden of disease (mildly disabled, short disease duration) are more likely to incur high relapse costs, predominantly due to higher indirect costs. These patients are more frequently employed, resulting in higher costs due to sick leave. Our results complement the findings of O'Brien et al., who showed that relapse costs varied with relapse severity [11].

A recent systematic review found that the most notable increase in relapse costs were associated with inpatient treatments, physician consultations, informal care, and sick leave [31]. With regard to our analysis, we confirm these results. Inpatient treatment during a relapse might be indicative of a severe relapse [10, 11]. In the investigated population inpatient care costs were lower than previously assumed [14]. This could partly be explained by the inclusion criteria, which require patients to be treated with DMTs. DMTs can affect the disease course by slowing disease progression and reducing the frequency and severity of relapses [32–35]. Fingolimod in particular has been shown to reduce healthcare resource utilization during relapses [33].

Despite the increase in resource costs during relapses, we found that resource cost utilization decreases in the post-relapse phase. However, costs partially remained above the initial cost level. Interestingly, this was particularly

Fig. 2 Quarterly costs (in €) of direct and indirect resource items before, during, and post relapse in relapse active patients (no RAW=457; RAW=150). Increases in costs are mainly due to inpa-

tient stays and work absenteeism. *Prior relapse* 3 months before relapse quarter, *during relapse* relapse quarter, *post relapse* 3 months after relapse quarter. RAW relapse-associated worsening

observed in patients with RAW for resources that are notably increased during periods of relapses (inpatient stays, physician consultations, informal care, and sick leave). This might indicate an incomplete recovery with residual disability [28, 36]. This result is in line with recent findings showing the high frequency of post-relapse residual disability [37].

Our analyses provide valuable information about the diverse economic impact of MS and thus might help decision makers to allocate scarce resources. Furthermore, in the context of economic evaluation, the results have the potential to increase the validity of cost-effectiveness assessments of innovative therapies in relapsing MS. Given the large number of available and upcoming MS therapies of varying effectiveness and costs, economic evaluations become even more relevant.

4.1 Limitations

Our relapse costs calculation is based on patient-reported resource utilization. To increase the validity of our results we calculated the relapse costs on an interindividual and intraindividual basis. In the interindividual calculation we compensated for variation between patients with and without relapses by applying PS matching. PS matching is a powerful technique to reduce imbalances in observable outcomes between populations. However, PS matching cannot address unknown or unmeasured differences, which might partially explain the lower relapse costs in the intraindividual as compared to the interindividual calculation. Furthermore, we did not include corticosteroid medication costs, which could have led to an underestimation of relapse costs.

5 Conclusion

For the case of MS, relapses significantly increased the societal economic burden. In particular, patients with a recent diagnosis and a mild disability incur higher relapse costs. In patients with RAW, relapse-associated resource costs remain elevated in the post-relapse period, indicating the need for treatment of residual disability. Our results suggest that it is necessary to incorporate patients' disease characteristics to appropriately assess relapse costs in economic evaluations and to optimize the provision of care from a clinical and societal perspective.

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Author Contributions NHN wrote the first manuscript. DS, NHN, and RH contributed substantially to the statistical analysis. All authors made substantial contributions to study conception and design and the interpretation of the data. All authors reviewed the manuscript and approved the manuscript for publication.

Data Availability Statement The data can be provided by the authors upon reasonable request, with the permission of Novartis Pharma GmbH and after receipt of a signed confidentiality agreement.

Compliance with Ethical Standards

Conflict of interest NHN has received funding for research from Novartis. DS has nothing to disclose. RH has received speaker fees from Sanofi and travel grants from Celgene. BE is an employee of Novartis. TZ received personal compensation from Almirall, Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, and Teva for consulting and speaking services, and he is the section editor for *BMC Neurology*. Additionally, he received financial support for research activities from BAT, Biogen Novartis, Teva, and Sanofi.

Ethical approvals Approval for PANGAEA and PEARL were obtained from independent, local, competent ethics committees.

Informed consent All patients provided written informed consent for the collection of clinical and health economic information.

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