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Explaining temporal trends in annualized relapse rates in placebo groups of randomized controlled trials in relapsing multiple sclerosis: Systematic review, meta-analysis and meta-regression

INAUGURAL – DISSERTATION

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vorgelegt von
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1 Introduction

1.1 Aim of this study

Across randomized controlled trials (RCTs), a downward trend in trial annualized relapse rates (ARRs) of placebo patients has recently been observed [Nicholas et al. 2011a; Inusah et al. 2010]. The trial ARRs of placebo patients improve significantly and increasingly so, although they receive no active agent [Nicholas et al. 2012]. This trend has severe implications: The inter-trial comparability of earlier and later trials is disputed [Nicholas et al. 2011a]. Consequently this complicates the comparison of new products with established competitors in lack of head-to-head data [Nicholas et al. 2011a]. In addition, new trials will require bigger sample sizes in order to achieve comparable statistical power [Nicholas et al. 2011a].

The aim of this dissertation is the description of this yet unexplained downward trend in placebo trial ARR and to investigate potential causal factors. It uses published, peer reviewed RCTs from 1982 to 2012 and analyzes factors such as patient baseline characteristics, eligibility criteria and other study design features, investigating possible factors contributing to this phenomenon.

1.2 Statement of authorship

The subject of this dissertation was a suggestion of my doctoral advisors, Prof. Dr. sc. hum. T. Friede (TF), head of the Institute of Medical Statistics (German: Institut für Medizinische Statistik) at University Medical Center Göttingen and PD Dr. phil. S. Straube from the Institute of Occupational, Social and Environmental Medicine at University Medical Center Göttingen, in 2011. Both acted as co-supervisors throughout the whole process.

I alone am responsible for the introduction, the literature search and the collection of data – although all data was later double-checked by either of three colleagues from the Institute of Medical Statistics, namely Dr. phil. C. Röver (CR), S. Schneider (SCH) and M. Butter (MB). I am also responsible for the data analysis, although I created the graphics mostly with assistance from CR, who wrote the software codes for the meta-regression, the forest and bubble plots. I received valuable insight from CR and TF on statistical questions more than once. TF, SS and CR advised me on the discussion, though I am responsible for the version proposed here.

Some of the findings presented in this dissertation were published as a poster (see appendix) during the 28th congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) from 10 – 13 October 2012 in Lyon, France, in collaboration with Dr. R. Nicholas FRCP (RN) at the Imperial College Healthcare NHS Trust in London, UK. The poster's abstract was published in the *Multiple Sclerosis Journal* [Steinvorth et al. 2012]

Time trends in baseline characteristics and eligibility criteria in trials in relapsing multiple sclerosis

Steinvorth SM, Nicholas R, Röver C, Schneider S, Straube S, Friede T

Some findings presented in this dissertation were published in the *Multiple Sclerosis Journal* in collaboration with RN [Steinvorth et al. 2013]:

Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression

Steinvorth SM, Röver C, Schneider S, Nicholas R, Straube S, Friede T

1.3 Multiple sclerosis

Multiple sclerosis (short: MS; Latin: Encephalomyelitis disseminata) is a chronic inflammatory autoimmune disease, which so far remains incurable. It is the most common demyelinating disease of the central nervous system (CNS) and the leading cause of non-traumatic disability among young adults in the United States of America [Wakerley et al. 2012; European Medicines Agency 2006; Fox et al. 2006]. The key diagnostic criterion of MS is the dissemination of demyelinating CNS lesions both in time and space [Polman et al. 2011]. The etiology of MS is unknown, there is however evidence of a combination of genetic and environmental factors [Wakerley et al. 2012].

1.3.1 Epidemiology

The median incidence of MS worldwide is estimated at 2.5/100,000 [World Health Organization and Multiple Sclerosis International Foundation 2008] and is speculated to be increasing, a notion which so far proved difficult to substantiate [Orton et al 2006]. The female to male ratio in incidence of MS is increasing [Trojano et al. 2012; Koch-Henriksen and Sørensen 2010; Alonso and Hernán 2008; Orton et al. 2006]. Global prevalence is estimated at 30/100,000 worldwide [World Health Organization and Multiple Sclerosis International Foundation 2008], with a wide range of variability in different regions; Germany for instance has a MS prevalence of 149/100,000 while the American continents report a combined prevalence of 8.3/100,000 [World Health Organization and Multiple Sclerosis International Foundation 2008]. Possible geographical patterns of epidemiological data, such as the hypothesis of a global latitude gradient with lower prevalence seen closer to the equator, are currently subject of scientific discussion, especially in respect to unanswered etiological questions [O'Gorman et al. 2012].

1.3.2 Pathogenesis, clinical symptoms and phenotypes

The formal pathogenesis of MS is presumed to be an immune dysregulation, predominantly involving T-lymphocytes [Hafler 2004; Wakerley et al. 2012]. T-cells that were primed in the peripheral blood recognize components of the myelin sheaths as an antigen, subsequently releasing a number of cytokines and thus activating macrophages and B-lymphocytes [Wakerley et al. 2012]. This results in the destruction of oligodendrocytes that build myelin sheaths, described as *demyelination*. Although the local inflammation causing the demyelination eventually resolves and remyelination sets in, damage to the underlying nerve fibres can not always be escaped [Wakerley et al. 2012].

Demyelination affects the ability of proper neuronal signal conduction [Wakerley et al. 2012; McDonald and Sears 1970], oftentimes leading to an acute exacerbation of symptoms, known as a *relapse*. Symptoms can also develop progressively over time, without an abrupt onset [Deutsche Gesellschaft für Neurologie 2012; Polman et al. 2011; Poser 1983].

These symptoms vary as much as the locations of the CNS lesions. Common symptoms include numbness, paresthesia, weakness, spasticity, dyscoordination, visual loss, binocular diplopia, bladder dysfunction, bowel dysfunction, and sexual dysfunction, as well as cognitive impairments, depression and fatigue [Fox et al. 2006].

A relapse is defined as the occurrence of one or more symptom, lasting at least 24 hours, not explicable by fever or infection, and preceded by a relatively stable or improving neurologic state of at least 30 days, as reported by the patient or objectively observed [Deutsche Gesellschaft für Neurologie 2012]. However, while some MS patients present only relapses and others only progressively developing symptoms, some do present both.

Lublin and Reingold defined four standardized disease courses to distinguish between clinical phenotypes [Lublin and Reingold 1996]:

Relapsing-remitting MS (RRMS)

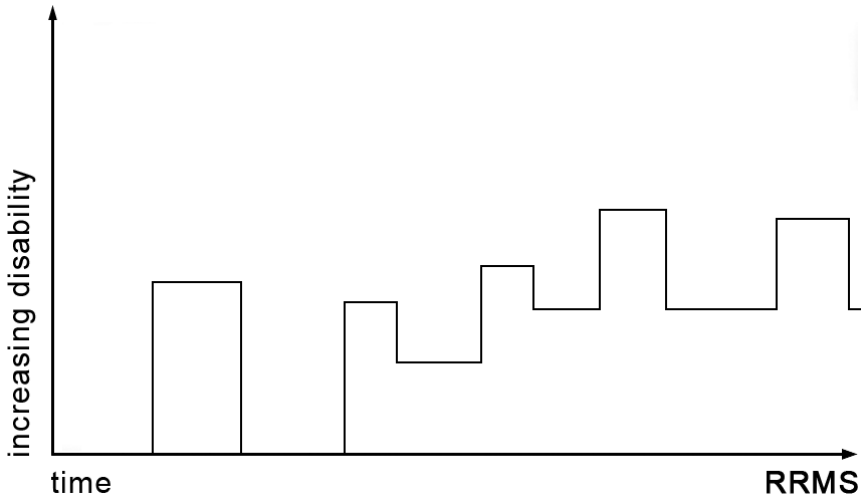

Figure 1: RRMS [Lublin and Reingold 1996, p908, modified]
The axis of abscissae represents time, the axis of ordinates the level of the patient's disability.

"*The defining elements of RRMS (also: exacerbating-remitting MS) are episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course between attacks*" **[**Lublin and Reingold 1996, p908]. About 85% of MS patients experience this course during disease onset [Fox et al. 2006].

Secondary-progressive MS (SPMS)

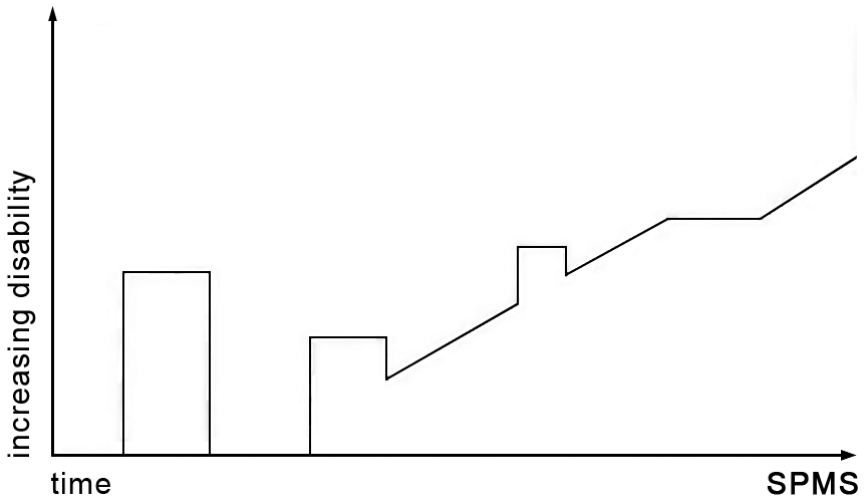

Figure 2: SPMS [Lublin and Reingold 1996, p909, modified]
The axis of abscissae represents time, the axis of ordinates the level of the patient's disability.

After an initial relapsing-remitting disease course, neuronal functioning begins to progressively worsen between relapses. Eventually, the disease progresses with or without occasional relapses, minor remissions, and plateaus [Lublin and Reingold 1996]. 50% of all RRMS patients eventually develop SPMS within ten years [European Medicines Agency, 2006].

Primary-progressive MS (PPMS)

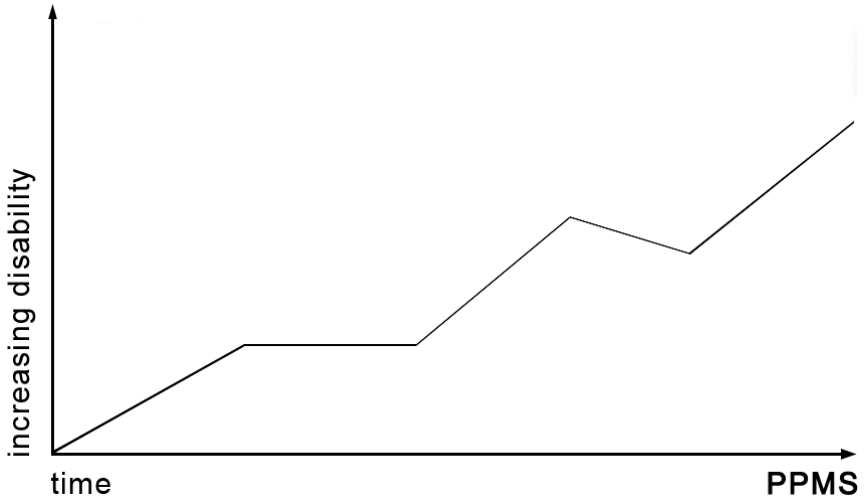

Figure 3: PPMS [Lublin and Reingold 1996, p909, modified]
The axis of abscissae represents time, the axis of ordinates the level of the patient's disability.

Nearly continuous „*disease progression from onset of the disease with occasional plateaus and temporary minor improvements allowed*" [Lublin and Reingold 1996, p908].

Progressive-relapsing MS (PRMS)

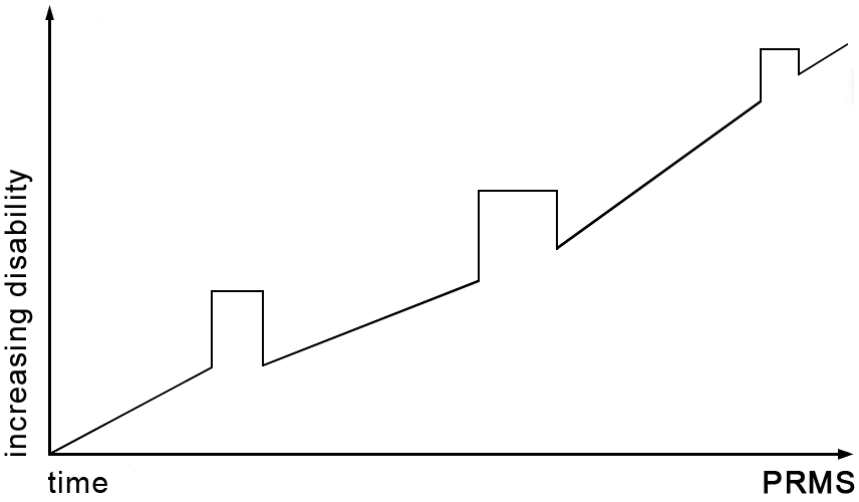

Figure 4: PRMS [Lublin and Reingold 1996, p910, modified]
The axis of abscissae represents time, the axis of ordinates the level of the patient's disability.

„*Progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing disease progression"* [Lublin and Reingold 1996, p909]. However, the German Society of Neurology (German: Deutsche Gesellschaft für Neurologie) does not list this disease course in their diagnostic guideline [Deutsche Gesellschaft für Neurologie 2012].

The term *Relapsing MS* (RMS) is defined by the presence of relapses, even though it is lacking a consistent definition: Some trials explicitly investigating *Relapsing MS* included only patients with RRMS and SPMS (for example Saida et al. 2012; study ID #56), some also included patients with PRMS (O'Connor et al. 2011; study ID #53), others did not specify what was meant by the term (Jacobs et al. 1996; study ID #12). In the following, the term is referred to as the subsumption of all phenotypes of confirmed MS that share the occurrence of relapses. In reference to the definitions by Lublin and Reingold, that includes RRMS, SPMS and PRMS.

1.3.3 Treatment

There is yet no curative approach in the treatment of MS. Therefore disease management remains the main objective in therapy development [European Medicines Agency 2006]. This includes shortening the duration of relapses, alleviating the severity of the symptoms, preventing the occurrence of relapses, delaying the long-term accumulation of disability, and/or improving residual neurological impairment [European Medicines Agency 2006].

A number of therapies have achieved some of these goals in clinical trials. The use of high-dose corticosteroids, for instance, is recommended in the case of an acute relapse [Deutsche Gesellschaft für Neurologie 2012; Multiple Sclerosis Therapy Consensus Group 2008]. Interferon-beta is recommended as a first-line therapy in RMS and CIS [Multiple Sclerosis Therapy Consensus Group 2008]. Glatiramer Acetate is recommended in RRMS and CIS [Multiple Sclerosis Therapy Consensus Group 2008]. Other pharmaceuticals include Natalizumab, Fingolimod, Mitoxantrone and Cyclophosphamide, which are recommended as second-line or escalating therapies under specific restrictions [Multiple Sclerosis Therapy Consensus Group 2008]. Most of these therapies have an effect on relapses, particularly their frequency and/or severity [Nicholas et al. 2011b; Deutsche Gesellschaft für Neurologie 2012; Multiple Sclerosis Therapy Consensus Group 2008]. As they target the immune response driving MS related CNS damage, they are subsumed as *disease modifying treatments*.

1.3.4 Guidelines on clinical investigation for MS treatments

Randomized, controlled trials (RCTs) represent the gold standard of clinical trials in evidence-based medicine. The Committee For Medicinal Products For Human Use (CHMP) of the European Medicines Agency provides guidelines on the clinical investigation of medicinal products in RCTs. The guideline for medicinal products for the treatment of MS [European Medicines Agency 2006] elaborates, among other details, on qualified outcome measures: It states that primary efficacy parameters should assess disability progression, and in patients with RMS also the frequency of relapses. The CHMP suggests the Annualized Relapse Rate (ARR) as the outcome of choice when assessing relapses and Kurtzke's Expanded Disability Status Scale (EDSS) when assessing progression of disability [European Medicines Agency 2006]. Parallel group, placebo-controlled study designs are currently favored among investigators, although in discussion [Nicholas and Friede 2012].

1.3.4.1 Expanded Disability Status Scale

The EDSS [Kurtzke, 1983] measures neurological functionality in seven distinct systems (pyramidal functions, cerebellar functions, brain stem functions, sensory functions, bowel and bladder functions, visual functions and mental functions) and processes them into ordinal grades ranging from 0.0, equivalent to a normal neurologic exam, over several grades of disability up to 10.0, equivalent to death due to MS. It has been criticized for its inadequate assessment of the upper limb functions and cognitive impairment [European Medicines Agency

2006], but none of the alternative disability assessments, such as the Multiple Sclerosis Functional Composite (MSFC) or the Multiple Sclerosis Severity Score (MSSS), could achieve similar support in the scientific community [D'Souza et al. 2008].

1.3.4.2 Annualized Relapse Rate

The ARR derives itself from a number of relapses divided by the follow-up time, normalized to the time of one year. It is used for patient groups by counting the total number of relapses of all group members and dividing the sum by the total accumulated patient-time in which these relapses occurred, normalizing it to the time of one year. Its main advantage over other relapse-related outcomes, such as the number of relapse-free patients or the time to first relapse, is that it takes more than just the first relapse into account [Wang et al. 2009]. Although ARRs in RMS patients were found to be age- and time-dependent [Tremlett et al. 2008], constant ARRs are assumed in the design and analysis of trials in RMS [Wang et al. 2009].

In this study, the term *trial ARR* refers to the ARR measured over the course of the trial, from randomization to the end of the trial. The term *pre-trial ARR* refers to the ARR before commencement of the trial at baseline.

2 Methods

2.1 Strategy

The first aim of this study was an analysis of ARRs across peer reviewed publications to answer the question of the described downward trend can be confirmed in a different, preferably larger set of studies than those it has previously been observed in. After confirmation of such a downward trend, this study examined other factors and traced other temporal trends that might be associated with the phenomenon in question. Those factors that demonstrated statistically significant temporal trends were then further analyzed in a meta-regression, in order to investigate a potentially causal relationship with the downward trend in trial ARR.

2.2 Literature search

The literature search used three scientific bibliographic online data bases (The Cochrane Library, Web of Science, Medline/PubMed), aiming to identify placebo-controlled, double-blind RCTs in MS with data on trial ARR or, alternatively, data that allowed trial ARR to be calculated.

The Cochrane Library

The search conducted in the Cochrane Library (URL: http://thecochranelibrary.com/) yielded 88 hits for the search terms *MS* in Title, Abstract or Keywords, *relapsing* in Title, Abstract or Keywords, *placebo* in Title, Abstract or Keywords and *rate;*

143 results for the search terms *multiple sclerosis* in Title, Abstract or Keywords, *patients* in Title, Abstract or Keywords, *placebo-controlled* in Title, Abstract or Keywords, *remitting* in Title, Abstract or Keywords and *double-blind* in Title, Abstract or Keywords;

and 15 results for the search terms *multiple sclerosis* in Title, Abstract or Keywords, *exacerbation rate* in Title, Abstract or Keywords, *clinical* in Title, Abstract or Keywords, *reduction* in Title, Abstract or Keywords, and *control* in Title, Abstract or Keywords.

Web of Science

The search in Web of Science yielded 320 hits for the search terms *relapsing* in Topic, *placebo* in Topic, and *lesion* in Topic.

PubMed

The Medline/PubMed search [URL: http://www.ncbi.nlm.nih.gov/pubmed/] produced 120 hits for the search terms *multiple sclerosis* in Title or Abstract, *relapse rate* in Title or Abstract, and *placebo* in Title or Abstract;

54 results for the search terms *multiple sclerosis* and *relapsing* and *placebo* in records from *2011/09/20* to *3000* in Date – Publication. This last search string was entered at a later point in time than the first to update the resulting trunk of trials at the end of the data acquisition period.

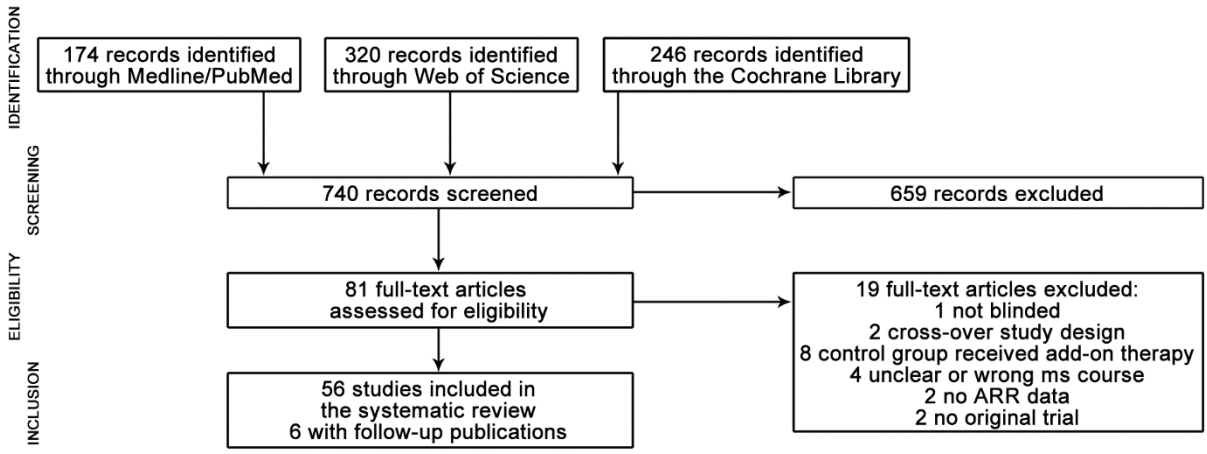

Figure 5: Flowchart of the literature search

All multiple entries, trials that were not double-blind, placebo-controlled RCTs in RMS, cross-over trials, non-human trials, trials where the control group received a form of active therapy (i.e. trials of add-on therapies) and open label extension studies of RCTs were excluded after exploration of the abstract or, if that proved inconclusive, the full text of the paper.

2.3 Acquisition of data

As a general procedural precept, mean values were extracted along with standard deviations (SD), or median values and interquartile ranges (IQR), when available. Where standard deviations were not available, they were calculated from p-values, standard errors (SE), confidence intervals (CIs) or t-statistics [Higgins and Green 2011, Part 2, Chapter 7.7: Extracting study results and converting to the desired format]. All extracted data from the papers were verified by either of three colleagues in the Institute of Medical Statistics (CR, SCH or MB).

2.3.1 Outcome data

The following data, if available, were extracted from the papers:

- The trial ARR in placebo groups,
- the associated number of placebo patients,
- the duration of placebo-controlled follow-up.

If a trial ARR was not stated, it was calculated by dividing the total number of relapses by the number of patients in the placebo group, giving a mean relapse rate, and then extrapolating to an annualized relapse rate by correcting for the time over which relapses were observed. When an adjusted rate was given, i.e. adjusted to age, sex or other parameters, as well as an unadjusted rate, the latter was preferred. Whenever trials distinguished between different intensities of relapses, the total sum of relapses was counted irrespective of severity. For ARRs without a quoted standard error, errors based on a Poisson approximation were derived, assuming a variance equal to the mean value.

In one instance [Miller et al. 2012] one data point (the standard deviation of the trial ARR of the placebo group) seemed implausible to the author and his supervisors. Since no published correction could be found and the authors of the publication in question did not reply to a request to clarify this point, this value was omitted.

2.3.2 Oxford Quality Scale

The Oxford Quality Scale (short: OQS; also sometimes called Jadad scale) is the most commonly used, most frequently cited scale to assess the quality of RCTs [Olivo et al. 2008]. It was originally developed by Jadad and colleagues [Jadad et al. 1996] and evaluates RCTs with regard to their documentation of randomization, blinding procedures and withdrawals or drop-outs on an ordinal scale between 0 and 5.

The score on the OQS was assessed for all papers included in this study. If a paper described the method for randomization in detail and it was appropriate, 2 points were given; if randomization was merely stated, 1 point; no points, if randomization was not mentioned at all or described, but inappropriate [Jadad et al. 1996]. The procedure for double blinding was analogous [Jadad et al. 1996]. If a paper described the number of drop-outs or withdrawals along with the reasons for the drop-out/withdrawal, 1 point was given [Jadad et al. 1996], resulting in a score range of the OQS between 0 and 5 points.

2.3.3 Study design features

Data on eligibility criteria

The following data, if available, were extracted from the papers:

- The number of eligibility criteria,
- the number of words and characters describing these criteria,
- trial inclusion criteria concerning age,
- trial inclusion criteria concerning pre-trial ARR,
- trial inclusion criteria concerning scores on the EDSS,
- trial inclusion criteria concerning the time since the last relapse,
- trial inclusion criteria concerning the time since the last use of high-dose steroids.

For the count of eligibility criteria, all inclusion criteria were counted, unless they were mutually exclusive, and all exclusion criteria were counted, unless they matched any inclusion criteria already counted, similar to the approach established by Clisant and colleagues [Clisant et al. 2012]. Only criteria applying to patients with RMS were counted. Having the correct diagnosis to be included to a study was counted as one criterion.

To determine the number of words or characters used to describe the eligibility criteria, all sentences or tables containing these criteria were copied into a word processing program (LibreOffice 3.5.2.2) and counted automatically. Features due to editing, such as spaces and bullets, were not included in the count. Captions of inclusion or exclusion criteria did count. When supplementary material offered more detailed information on eligibility criteria than the main publication, it was used instead of the latter.

Additional study design features

The following data, if available, were extracted from the papers:

- The number of treatment arms in the trial,
- the allocation ratio of recruited patients to these arms.

When the allocation ratio was not explicitly given in a paper, it was derived by the numbers of patients in the trial arms.

2.3.4 Patient characteristics at baseline

The following baseline data, if available, were extracted from the papers:

- Age,
- pre-trial ARR,
- score on the EDSS,
- duration of MS,
- the number of patients to whom these characteristics apply,
- the proportion of women among these patients.

Baseline characteristics were retrieved for the placebo group and across all groups of RMS patients. When baseline characteristics across all groups were not available, they were calculated by combining data provided for the individual treatment arms [Higgins and Green 2011, Part 2, Chapter 7.7: Extracting study results and converting to the desired format].

Where possible, data on RRMS patients were preferred over data on patients with other forms of MS. When the mean age at baseline was not given, it was calculated by adding the mean MS duration to the mean age at the onset of the disease, if provided. Baseline characteristics of patients randomized to treatment arms were preferred over characteristics describing only patients who actually received treatment.

If pre-trial ARR was not specified, but the number of relapses in a certain time period or a non-annualized relapse rate was, it was calculated in the same manner as the trial ARR (see above). If studies presented multiple pre-trial ARRs calculated over different time periods, all were extracted.

For ARRs without a quoted standard error (compare Section 10.2.), errors were derived based on a Poisson approximation, assuming a variance equal to the mean value.

2.4 Data analysis

For the purpose of all analyses of temporal trends, the year and month of publication was used, whereas in figures references were sorted by the year of publication and within it alphabetically, spread across the year in question, to allow for clarity. The resulting order is maintained throughout this dissertation, and each paper was assigned an identifying number.

When mean values were not given, available median values were used as a direct estimate instead, if they did not require extrapolation. Corresponding IQRs, if not equal to zero, were used to estimate SDs, assuming normal distributions. Values obtained in such a manner are indicated in the figures. Mean values with SDs had top priority, mean values with SDs estimated

from IQRs second, median values with SDs estimated from IQRs third priority, followed by solitary mean values and lastly solitary median values.

2.4.1 Outcome data

The natural logarithms of the trial ARR of placebo groups were modeled by Gaussian linear regression over time, weighted by the inverse standard error squared. For the means 95% CIs were calculated.

Unweighted linear regressions over time were calculated for:

- The duration of placebo-controlled follow-up,
- the number of patient years considered for the calculation of trial ARRs,
- the dispersion of trial ARRs in placebo groups, utilizing only variances based on stated data.

2.4.2 Oxford Quality Scale

The score on the Oxford Quality Scale was analyzed by unweighted linear regressions over time.

2.4.3 Study design features

Unweighted linear regressions over time were calculated for:

- The number of eligibility criteria,
- the number of words describing the eligibility criteria,
- the ratio of words per criterion,
- the number of characters describing the eligibility criteria
- the ratio of characters per criterion,
- the minimum pre-trial ARR for inclusion,
- the number of years considered for the calculation of pre-trial ARRs,
- the minimum age for inclusion,
- the maximum age for inclusion,
- the minimum score on the EDSS for inclusion,
- the maximum score on the EDSS for inclusion,

- the minimum number of days without relapse,
- the minimum number of days without the use of high-dose steroids,
- the number of treatment arms,
- the mean number of patients per treatment arm.

Inclusion criteria were omitted in analyses of individual items, when they appeared in a complex context that allowed alternative options to qualify in one measure or mutually exclusive options of different measures (For example: *Study inclusion required patients to have either two relapses in the last two years, or one relapse in the last six months, or two Gadolinium-enhancing lesions in the Magnetic Resonance Imaging (MRI) at baseline*). They were, however, still counted.

2.4.4 Patient characteristics at baseline

The natural logarithms of the pre-trial ARR of placebo groups and across all groups were modeled by Gaussian linear regression, weighted by the inverse SE squared. For the means, 95% CIs were calculated. When multiple pre-trial ARRs could be collected, those accounting for the longest period were used.

In all cases of multiple pre-trial ARRs, ARRs were stated for the time period one year before baseline and for the time period two years before baseline. From those, the pre-trial ARR of the year preceding baseline and of the second preceding year were derived [Higgins and Green 2011, Part 2, Chapter 7.7: Extracting study results and converting to the desired format]. The logarithmic ratios of these ARRs of different pre-trial time periods of equal length were investigated via a random-effects meta-analysis with inverse variance weighting. The combined estimates are reported along with 95% CIs and p-values testing the null hypothesis of no difference between the time intervals. Heterogeneity between studies is estimated and reported in terms of the heterogeneity measure I^2, which is the ratio of the between-trial variance and the total variance, alongside the p-values of the chi-square test of heterogeneity. Forest plots illustrating the ratios of the individual studies and the combined effect allow for visual comparison of the heterogeneity and provide an overview of the results.

Linear regressions over time, weighted by the inverse SE squared, taking all values with SEs into account, were calculated for the following baseline characteristics of the placebo groups and across all groups:

- Age,
- disease duration,
- score on the EDSS,
- gender.

2.4.5 Epoch analyses

As supportive analyses of the most important items, the mean values of four deliberate partitions of the 56 trials included in this study were compared, testing for possible trends that might have been concealed in the analysis of all studies over time. These analyses are referred to as epoch analyses. Recognizable points in trial history were chosen to subdivide the trunk of trials: The first cluster of trials comprised all trials up to the end of 1994, the second cluster all trials from the beginning of 1995 to the end of 2000, the third cluster all trials from the beginning of 2001 to the end of 2009, the fourth cluster all trials from the beginning of 2010 to today. The divisors in mind were 1995 as the year of the renowned IFNB trial (study ID #10), 2001 as the year of the influential Comi trial investigating Glatiramer Acetate (study ID #30) and 2010 as the year when large numbers of patients included to phase 3 studies became more common. The following items were analyzed in this manner:

- The trial ARR in placebo groups,
- the duration of placebo-controlled follow-up,
- scores on the Oxford Quality Scale,
- the number of eligibility criteria,
- the number of words describing the eligibility criteria,
- the number of characters describing the eligibility criteria,
- the minimum pre-trial ARR for inclusion,
- the number of years considered for the calculation of pre-trial ARRs,
- the minimum score on the EDSS for inclusion,
- the maximum score on the EDSS for inclusion,
- the minimum number of days without relapse,
- the minimum number of days without the use of high-dose steroids,
- the mean age in placebo groups and across all groups at baseline,
- the mean disease duration in placebo groups and across all groups at baseline,
- the mean score on the EDSS in placebo groups and across all groups at baseline,
- the mean pre-trial ARR in placebo groups and across all groups,
- the gender distribution in placebo groups and across all groups.

2.4.6 Statistical considerations

The level of statistical significance was set at α = 0.05. The p-value gives the probability of the test statistic reaching the observed or a more extreme value under the null hypothesis, i.e. the assumption that there is no correlation between the variable in question and the given data. If $p \leq \alpha$, rejection of the null hypothesis is justified for a given probability α of a type I error.

Statistical computing software (R version 2.14.2, URL: http://www.r-project.org/; Review Manager (RevMan) version 5.1, The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, URL: http://ims.cochrane.org/revman/) was used for all analyses and Figures 6 to 36.

2.4.6.1 Regression models

Typically, a regression model consists of an intercept plus the sum of a number of variables multiplied by individual coefficients [Kutner et al. 2005]:

$$y = \left(\sum_{i=1}^{n} a_i x_i\right) + b + \varepsilon$$

In this formula, y is the true trial ARR, n the number of variables included in the regression model, x_i any of the variables included – with a_i as the assigned coefficient, b the intercept and ε the residual error. In linear regression models for example, n is set to 1.

2.4.6.2 Meta-regression of statistically significant temporal trends

Finally, all statistically significant temporal trends were investigated in a meta-regression calculating to what extent they contributed to the temporal trend in trial ARRs. Here a more complex regression model was sought.

When there are v number of variables that might be included in the regression, the possible number of combinations and consequently the number of regression models is 2^v. For example, provided that $v = 10$, there would be $2^{10} = 1024$ different regression models that needed to be compared, in order to find the best one. To do that, use of the Bayesian information criterion (BIC) was made. The BIC is a criterion that offers a way to compare different regression models and choose the best of them:

$$\text{BIC} = -2 \cdot \ln(L) + n \cdot \ln(s)$$

In this case, s the number of studies analyzed, while n is the number of variables included in the regression model. The Likelihood L is a function that calculates how good a fit the regression model is, i.e. how likely the regression resembles the given data set it is supposed to model.

The best regression model is the one with the minimal BIC, which is minimized by increasing likelihood, but boosted by increasing numbers of included variables, therefore targeting a model

that explains as much as possible, yet simultaneously remaining as simple as possible [Kass and Raftery 1995, p790].

When the final regression model is chosen, the coefficient of determination R^2 allows quantifying the percentage to which the model explains the given data. It is calculated through the residual sum of squares divided by the total sum of squares [Kutner et al. 2005]:

$$R^2 \equiv 1 - \frac{\sum_{k=1}^{s}(y_k - f_k)^2}{\sum_{k=1}^{s}(y_k - \bar{y})^2}$$

In this formula, y_k is the given data value and f_k its regression-modeled value, $\bar{y}$ is the mean of the given data. This way R^2 is bound to be a value between one and zero, with $R^2 = 0$ showing no correlation between the regression model and the data set at all, and $R^2 = 1$ showing a perfect regression model, which would be able to explain each given value in the data set. Here, the given data values are the trial ARRs of each of the 56 studies included in this review.

3 Results

3.1 Literature search

A total of 56 randomized, placebo-controlled, double-blind clinical trials was identified, including a total of 14,792 patients, of which 5,380 had been randomized to placebo. Table 1 gives an overview of the studies and their assigned identification numbers. Tabulated summaries of the 56 trials are provided in the appendix (see Section 10.2).

Table 1: Studies included in the data analysis

Study ID No.	First authorship
#1	[Gonsette et al. 1982]
#2	[Mertin et al. 1982; Mertin et al. 1980]
#3	[Camenga et al. 1986]
#4	[Jacobs et al. 1987; Jacobs et al. 1986]
#5	[Hirsch et al. 1988]
#6	[Milanese et al. 1988]
#7	[Goodkin et al. 1991]
#8	[Bastianello et al. 1994]
#9	[Durelli et al. 1994]
#10	[The IFNB Multiple Sclerosis Study Group & the University of British Columbia MS/MRI Analysis Group 1995; the IFNB Multiple Sclerosis Study Group 1993]
#11	[Andersen et al. 1996]
#12	[Jacobs et al. 1996]
#13	[Lycke et al. 1996]
#14	[Fazekas et al. 1997]
#15	[Millefiorini et al. 1997]
#16	[Miller et al. 1997]
#17	[Van Oosten et al. 1997; Van Oosten et al. 1996]
#18	[Achiron et al. 1998]
#19	[Johnson et al. 1998; Johnson et al. 1995]
#20	[Noseworthy et al. 1998]
#21	[Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis Study Group 1998]
#22	[Deisenhammer et al. 1999]
#23	[Lenercept Multiple Sclerosis Study Group & the University of British Columbia MS/MRI Analysis Group 1999]
#24	[Myhr et al. 1999]
#25	[The Once Weekly Interferon for MS Study Group 1999]
#26	[Patti et al. 1999]
#27	[Romine et al. 1999]
#28	[Tubridy et al. 1999]
#29	[Brod et al. 2001]
#30	[Comi et al. 2001]
#31	[Bech et al. 2002]
#32	[Lewańska et al. 2002]
#33	[Miller et al. 2003]

Study ID No.	First authorship
#34	[Wroe 2005]
#35	[Filippi et al. 2006]
#36	[Kappos et al. 2006]
#37	[O'Connor et al. 2006]
#38	[Polman et al. 2006]
#39	[Broadley et al. 2008]
#40	[Comi et al. 2008]
#41	[Fazekas et al. 2008]
#42	[Garren et al. 2008]
#43	[Hauser et al. 2008]
#44	[Kappos et al. 2008]
#45	[Mostert et al. 2008]
#46	[Segal et al. 2008]
#47	[Barkhof et al. 2010]
#48	[Giovannoni et al. 2010]
#49	[Kappos et al. 2010]
#50	[Vollmer et al. 2010]
#51	[De Stefano et al. 2011; De Stefano et al. 2010]
#52	[Kappos et al. 2011]
#53	[O'Connor et al. 2011]
#54	[Comi et al. 2012]
#55	[Miller et al. 2012]
#56	[Saida et al. 2012]

3.2 Outcome data

3.2.1 Trial ARRs in placebo groups

As shown in Figure 6, trial ARRs in placebo groups decreased by 4.56% per year (95% CI: 3.24 – 5.89%). In the time span investigated, this accumulated to a decrease of nearly 1.5 relapses per year, starting with a rate of 2.0. This finding was expected, yet its dimension still impressive.

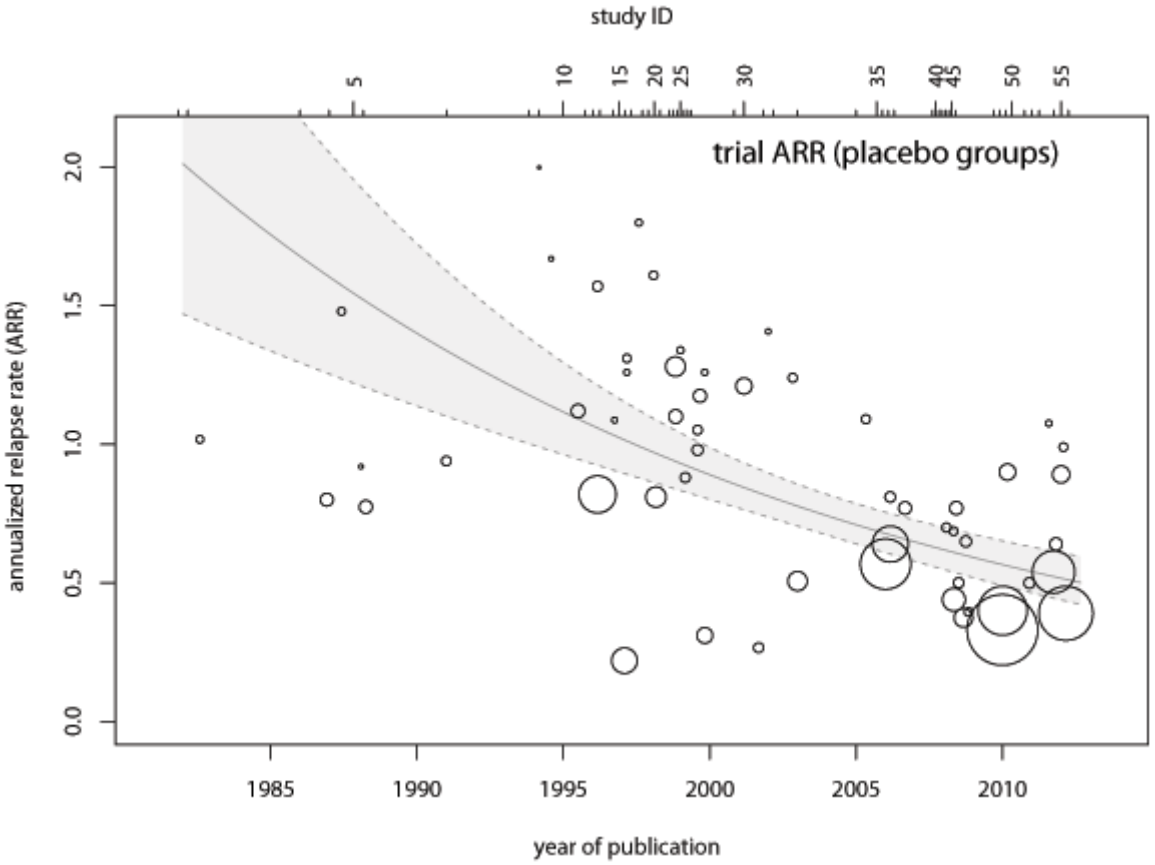

Figure 6: Trial ARR (placebo groups)
The axis of abscissae represents time, the axis of ordinates the trial ARR in placebo groups. Symbol sizes correspond to SEs; the inner gray trend line shows the result of the regression; the outer dashed lines serve as borders to the 95% CI highlighted in light gray.

3.2.2 Duration of placebo-controlled follow-up

The duration of placebo-controlled follow-up decreased yearly by 16 days (p-value = 0.006; coeff = -15.782 (95% CI: -26.923 – -4.641)) on average, as shown in Figure 7. Given that the trials included in the analyses were either phase II or phase III (phase II studies usually last from 6 – 9 months, phase III studies usually 1 - 2 years), and less than half of the trials made specifications to their phase, the visible decrease is likely to reflect both the emergence of more phase II studies in the later years, as well as a possible tendency toward shorter phase III studies.

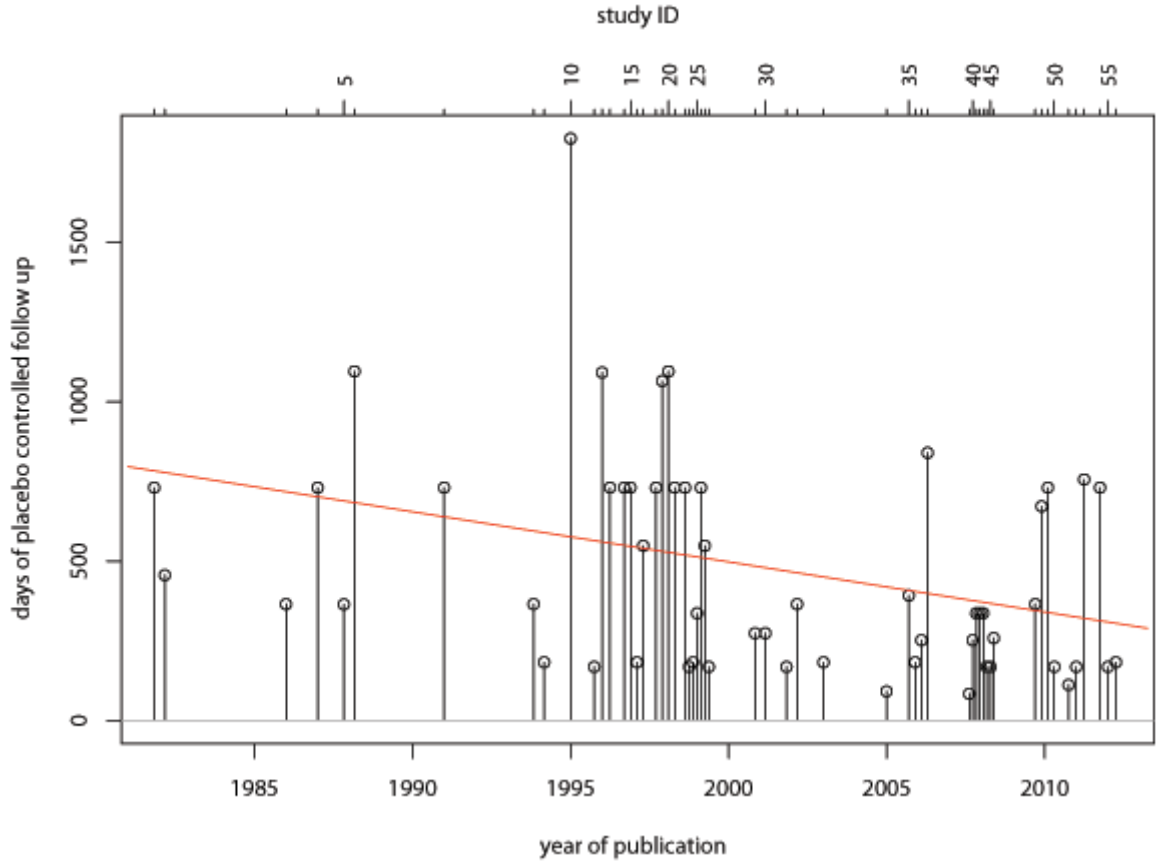

Figure 7: Duration of placebo-controlled follow-up in days
The axis of abscissae represents time, the axis of ordinates the duration of placebo-controlled follow-up. The red trend line shows the result of the linear regression.

3.2.3 Number of patient years considered for the calculation of trial ARRs

Changes in the number of patient years considered for the calculation of trial ARRs in placebo groups did not meet statistical significance (p-value = 0.051; coeff = 8.58 (95% CI: 0.15 – 17.01)). Since statistical significance was missed by a close 0.001, the upward trend indicated by the red line in Figure 8 may still be worth a glimpse.

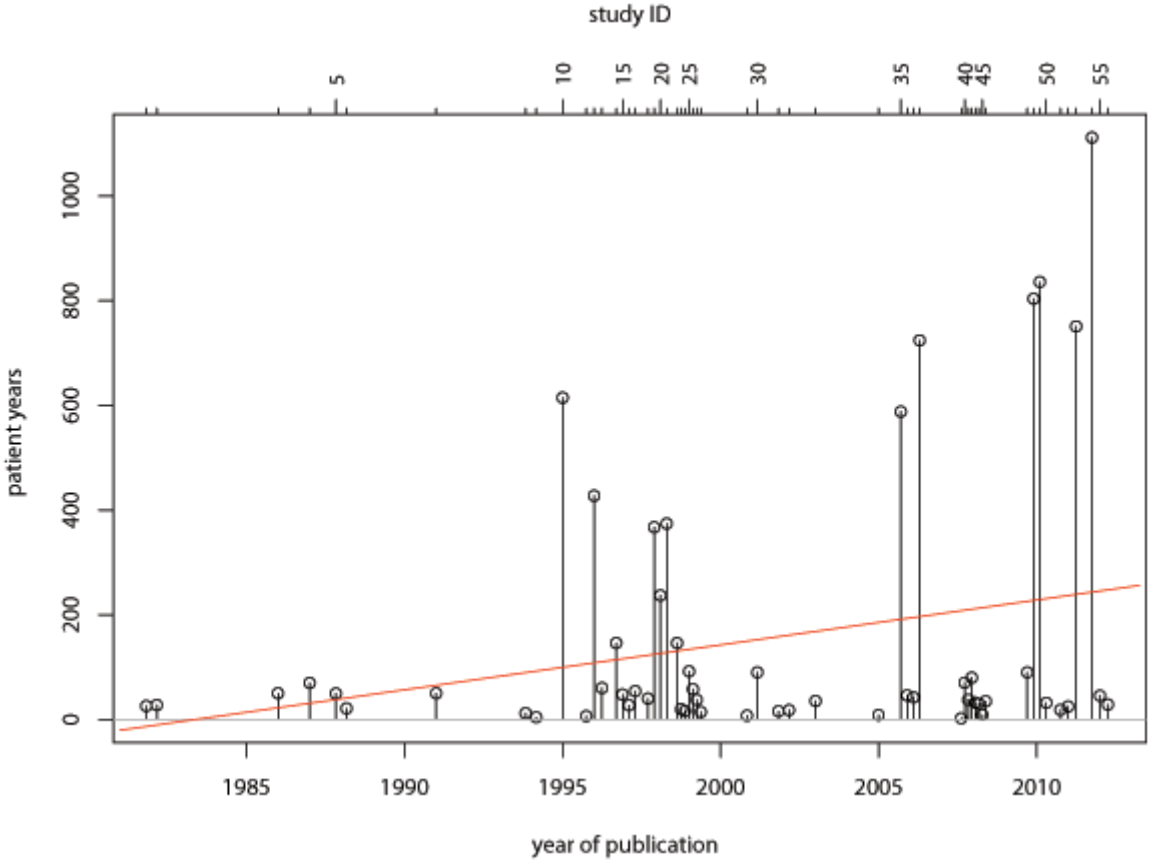

Figure 8: Number of patient years considered for the calculation of trial ARRs (placebo groups)
The axis of abscissae represents time, the axis of ordinates the number of patient years considered for the calculation of trial ARRs. The red trend line shows the result of the linear regression.

3.2.4 Dispersion of trial ARRs in placebo groups

Changes in the dispersion of trial ARRs, i.e. the variance divided by the mean value, did not reach statistical significance (p-value = 0.314; coeff = 0.03 (95% CI: -0.027 – 0.086)), as shown in Figure 9. The discussion will delve into this notion.

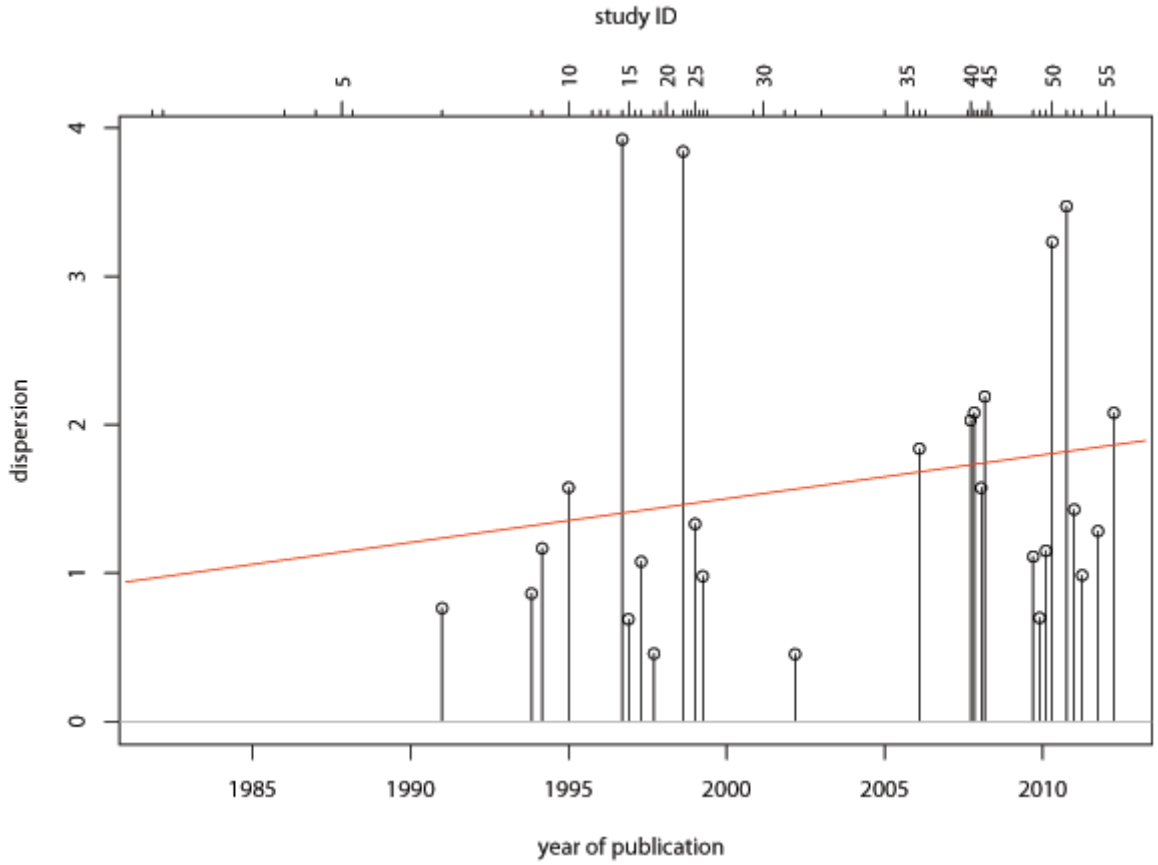

Figure 9: Dispersion of trial ARR (placebo groups)
The axis of abscissae represents time, the axis of ordinates the dispersion of trial ARRs. The red trend line shows the result of the linear regression.

3.3 Oxford Quality Scale

Scores on the OQS increased by half a point in 18 years (p-value = 0.022; coeff = 0.028 (95% CI: 0.004 – 0.051)) on average, despite the outlier in 2011 (study ID #51). As can be seen in Figure 10, most studies scored 4 or 5 points on the scale, which may be considered as rather good results.

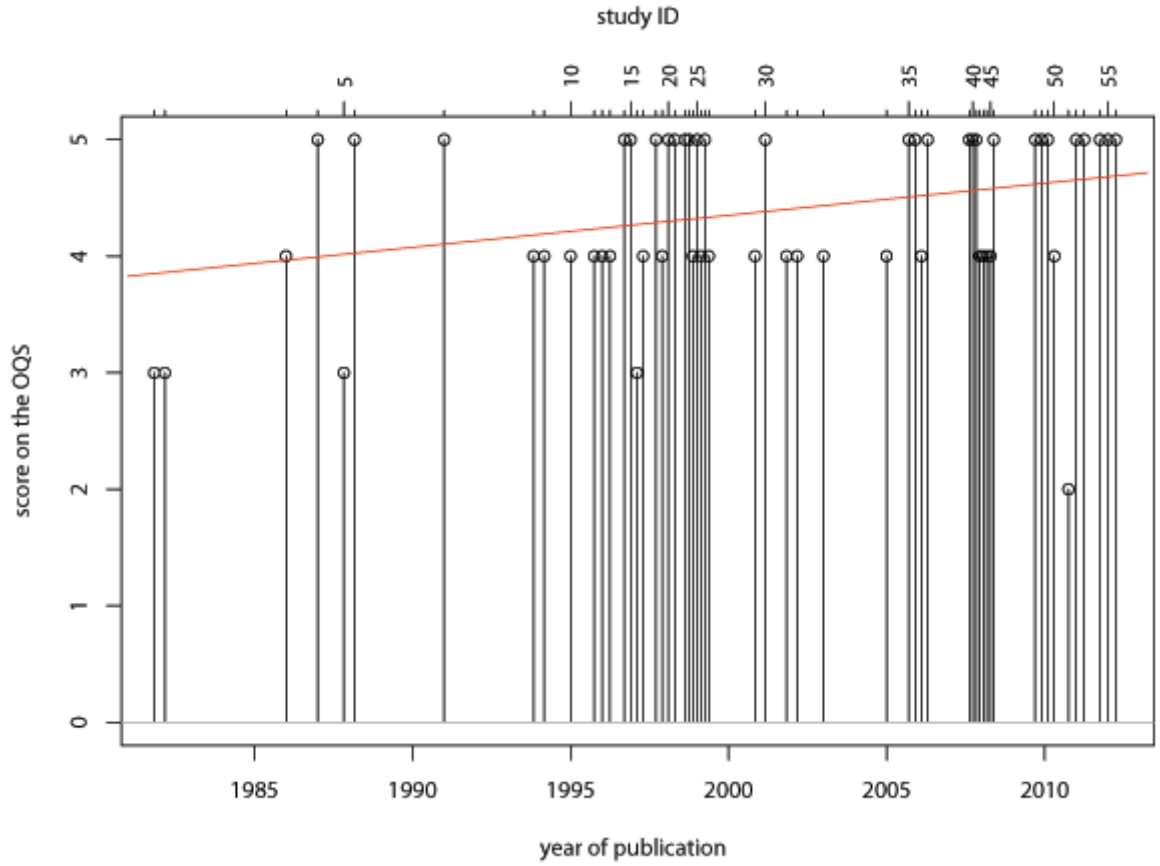

Figure 10: Scores on the Oxford Quality Scale
The axis of abscissae represents time, the axis of ordinates scores on the OQS. The red trend line shows the result of the linear regression.

3.4 Study design features

3.4.1 Data on eligibility criteria

Number of eligibility criteria

As shown in Figure 11, the number of eligibility criteria increased on average by three criteria every four years ($p<0.001$; coeff = 0.771 (95% CI: 0.392 – 1.151)). This may to a part reflect the growing understanding of the investigated interventions, a relation to the increasing quality in reporting is nonetheless likely to play a role.

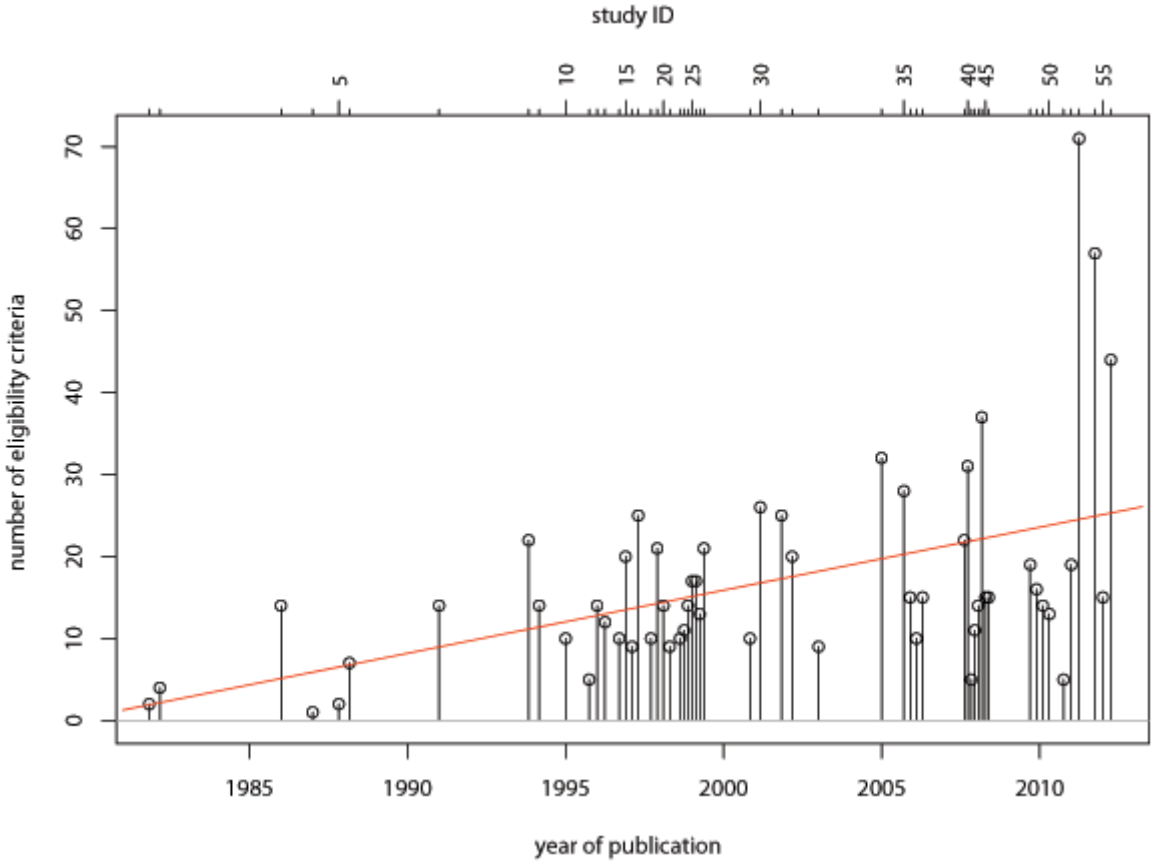

Figure 11: Number of eligibility criteria
The axis of abscissae represents time, the axis of ordinates the number of eligibility criteria. The red trend line shows the result of the linear regression.

Number of words describing the eligibility criteria

The number of words describing the eligibility criteria increased on average by 20 words every three years ($p<0.001$; coeff = 6.651 (95% CI: 3.372 – 9.93)), as visible in Figure 12. Given the increasing number of eligibility criteria, this was to be expected.

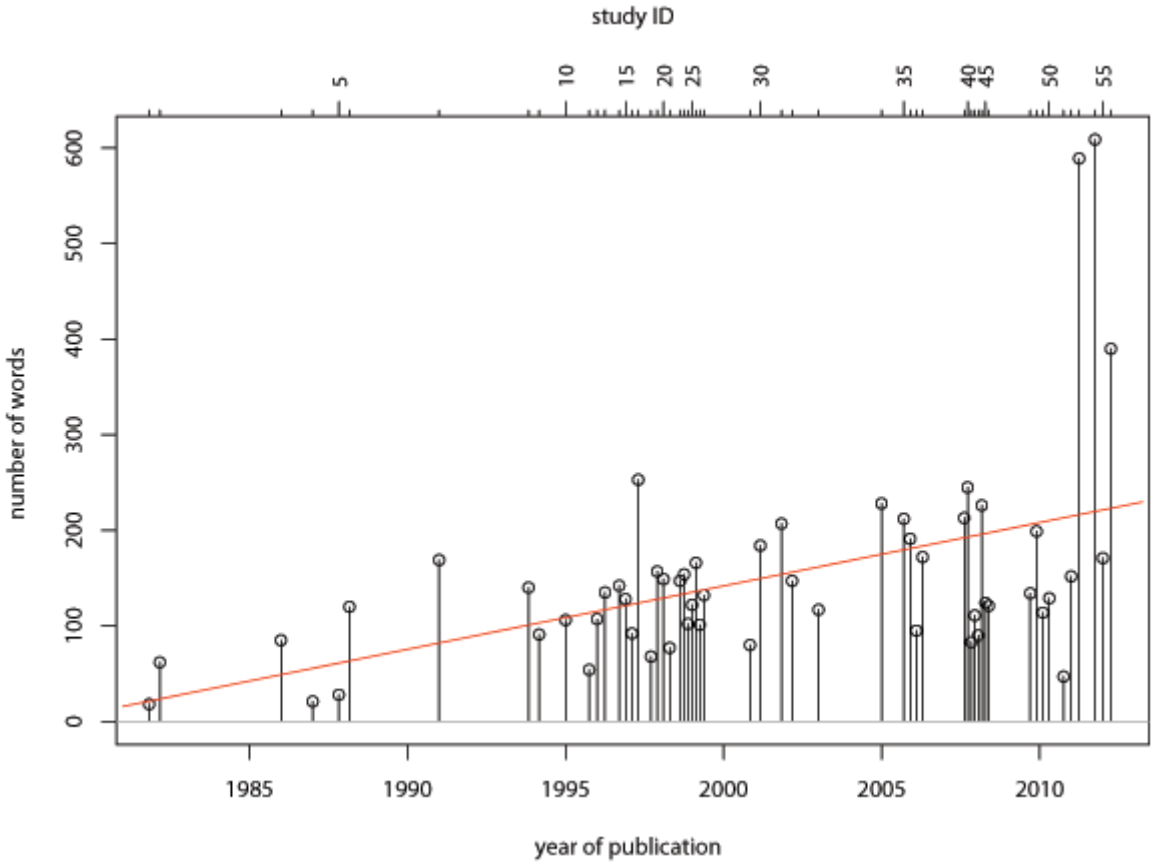

Figure 12: Number of words describing eligibility criteria
The axis of abscissae represents time, the axis of ordinates the number of words describing the eligibility criteria. The red trend line shows the result of the linear regression.

Words per eligibility criterion

The average ratio of words per eligibility criterion decreased by 1 word every 9 eligibility criteria (p-value = 0.039; coeff = -0.112 (95% CI: -0.215 – -0.008)), as shown in Figure 13. Plain listings of eligibility criteria are common and additional criteria oftentimes result in no more than one additional word, so the decrease was not unexpected.

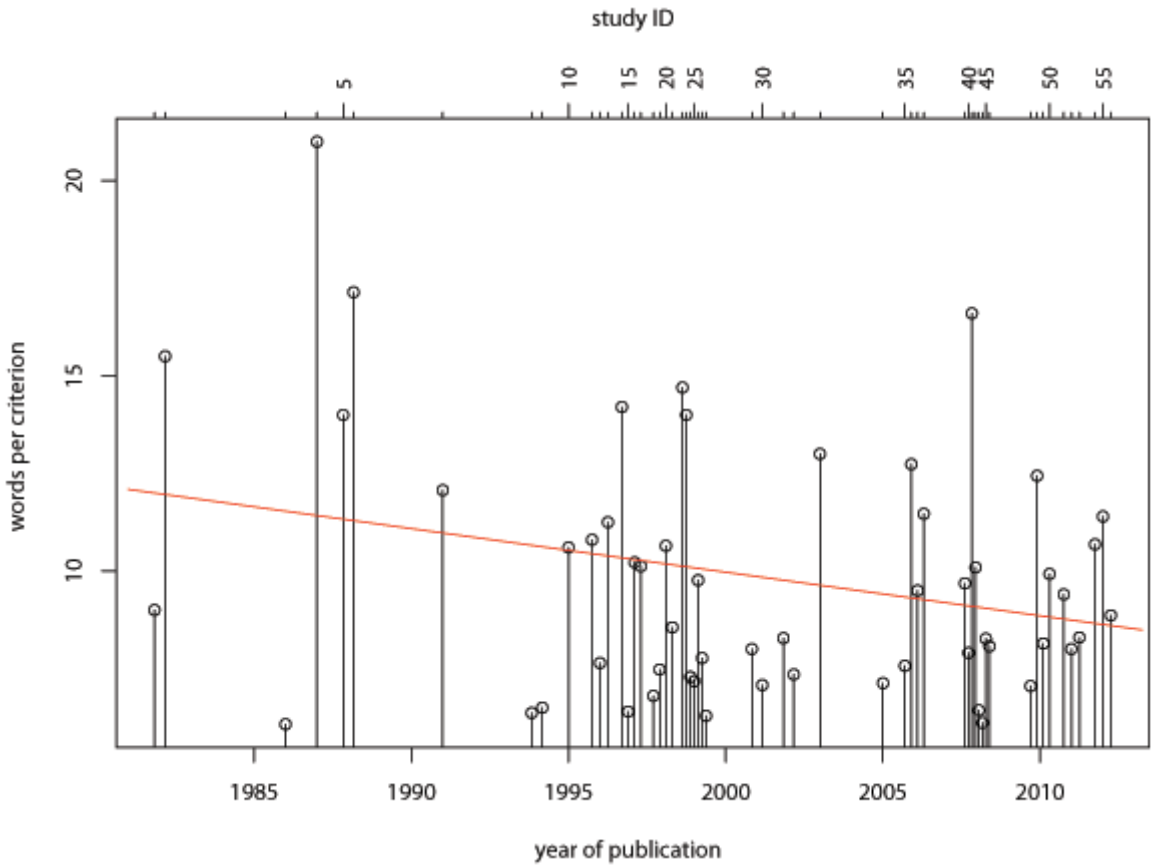

Figure 13: Ratio of words per eligibility criterion
The axis of abscissae represents time, the axis of ordinates the ratio of words per eligibility criterion. The red trend line shows the result of the linear regression.

Number of characters describing the eligibility criteria

As shown in Figure 14, the number of characters describing the eligibility criteria increased on average by 40 characters every year ($p<0.001$; coeff = 39.638 (95% CI: 20.109 – 59.168)). Given the increasing number of eligibility criteria, this was to be expected.

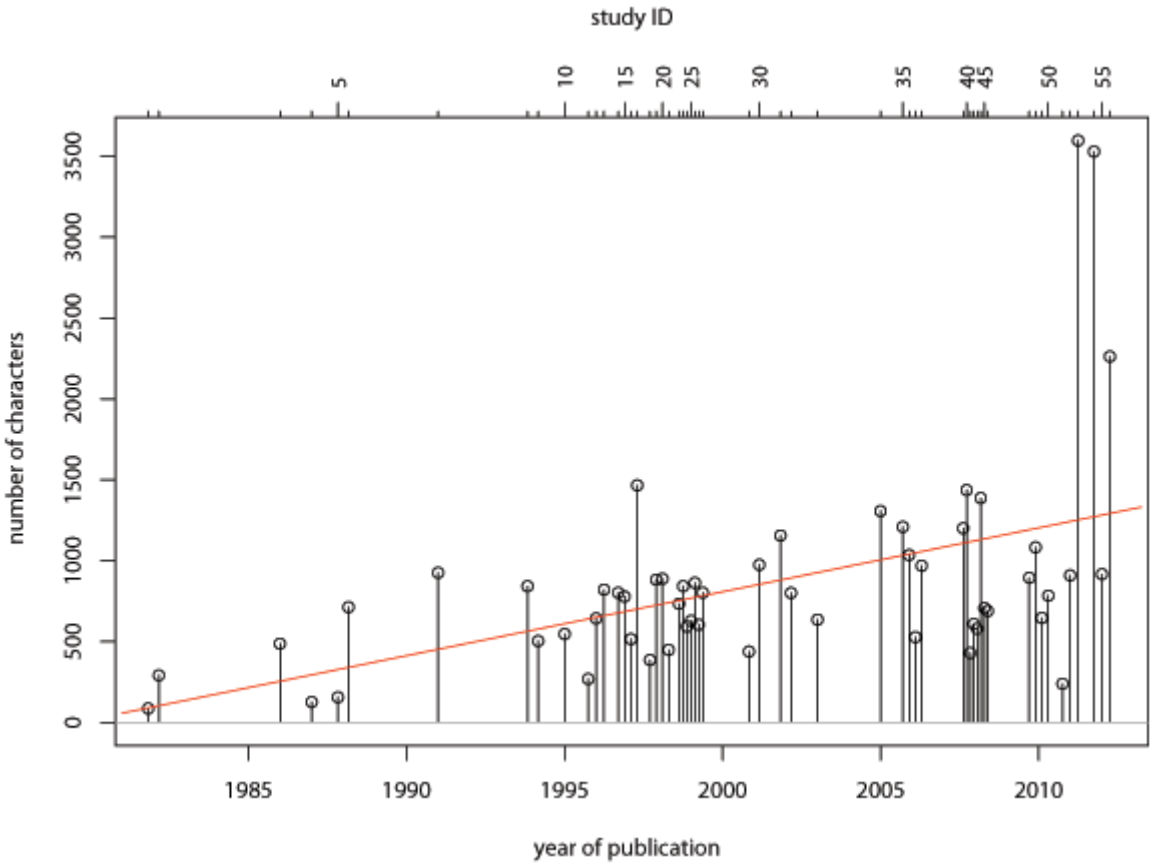

Figure 14: Number of characters describing eligibility criteria
The axis of abscissae represents time, the axis of ordinates the number of characters describing the eligibility criteria. The red trend line shows the result of the linear regression.

Characters per eligibility criterion

As shown in Figure 15, changes in the average ratio of characters per eligibility criterion did not reach statistical significance (p-value = 0.078; coeff = -0.523 (95% CI: -1.093 – 0.047)). Analogous to the ratio of words per eligibility criterion, this was expected.

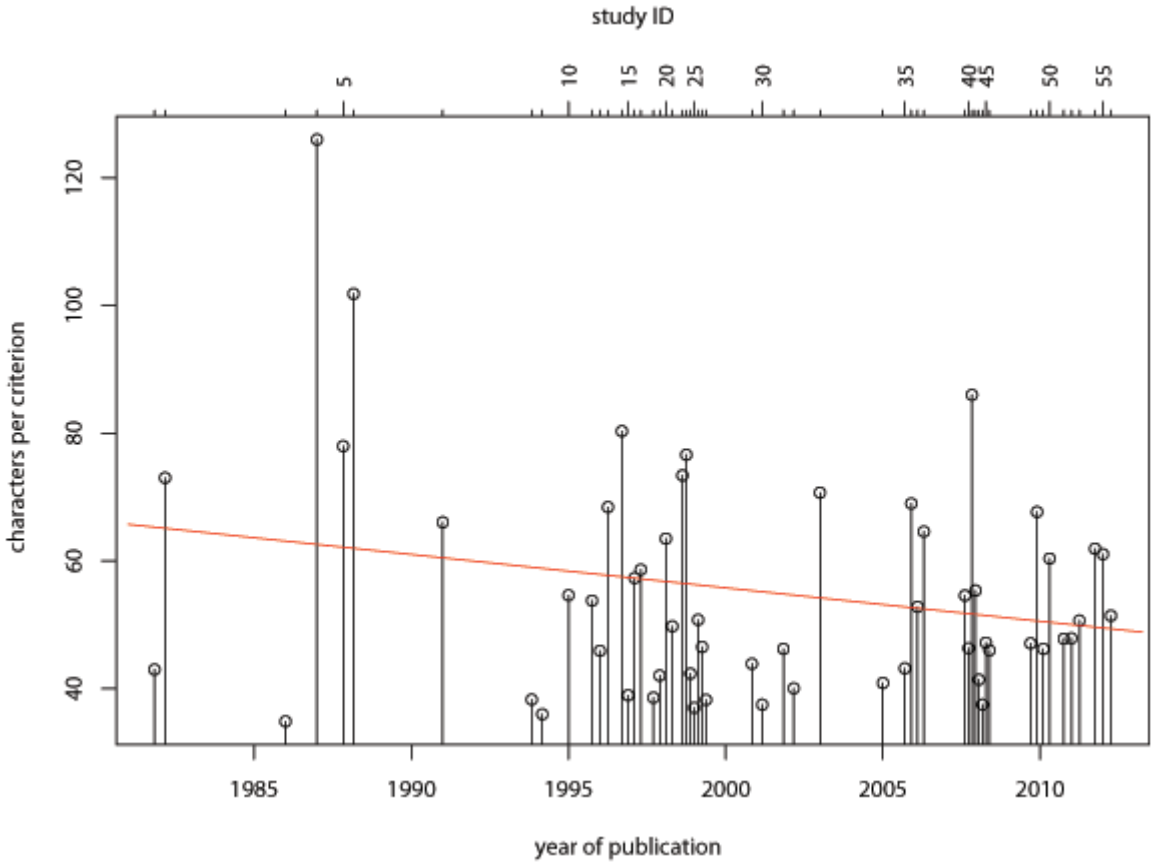

Figure 15: Ratio of characters per eligibility criterion
The axis of abscissae represents time, the axis of ordinates the ratio of characters per eligibility criterion. The red trend line shows the result of the linear regression.

3.4.1.1 Pre-trial ARR

Minimum pre-trial ARR for inclusion

Changes in the minimum pre-trial ARR for inclusion did not reach statistical significance (p-value = 0.582; coeff = 0.003 (95% CI: -0.008 – 0.013)). As easily seen in Figure 16, the minimum pre-trial ARR for inclusion remained roughly at one relapse per year.

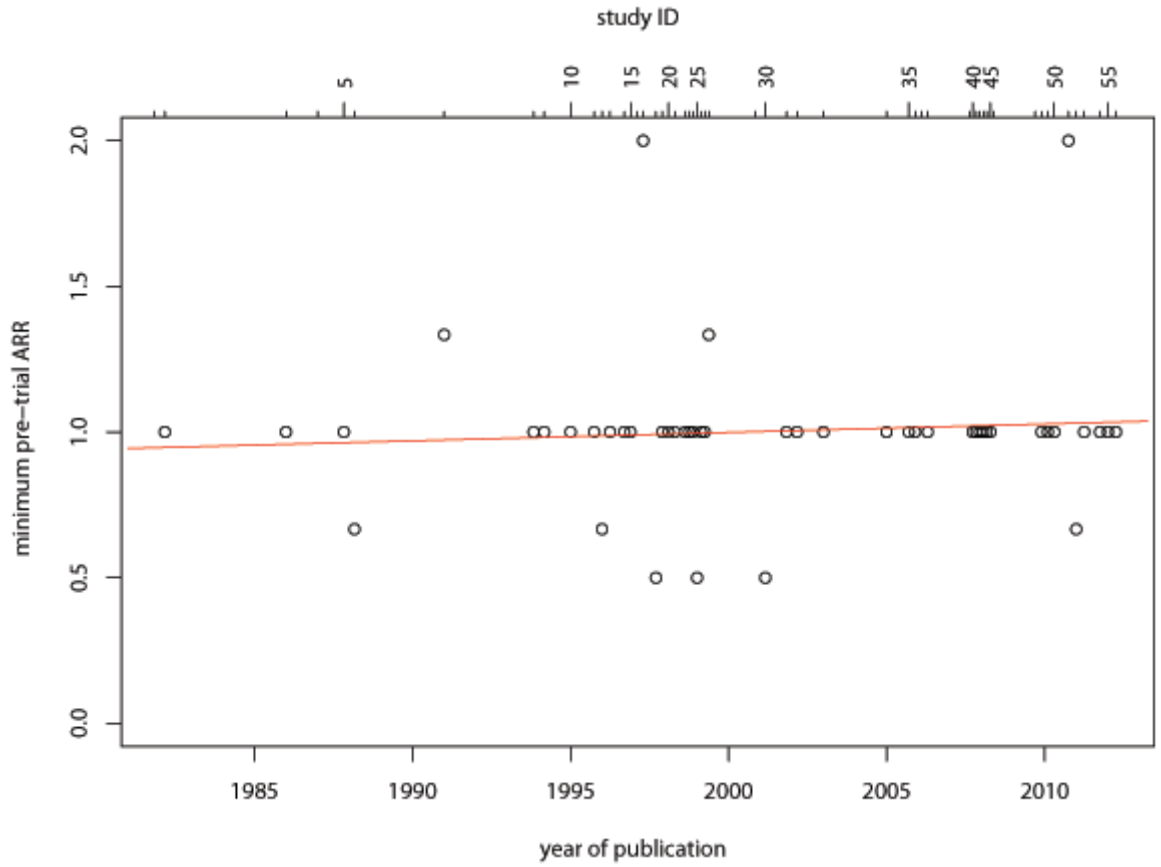

Figure 16: Minimum pre-trial ARR for inclusion
The axis of abscissae represents time, the axis of ordinates the minimum pre-trial ARR for inclusion to the study. The red trend line shows the result of the linear regression.

Number of years considered for the calculation of pre-trial ARR

The time period considered for the calculation of pre-trial ARR decreased by 18 days every year (p-value=<0.001; coeff = -0.049 (95% CI: -0.071 – -0.027)) on average, as shown in Figure 17. This was a rather remarkable finding; at the beginning of the investigated time period, the occurrence of relapses of recruit patients tested for eligibility was mostly inquired for the last two or three years before commencement of the trial, after 2005 inquiries for only one year became customary.

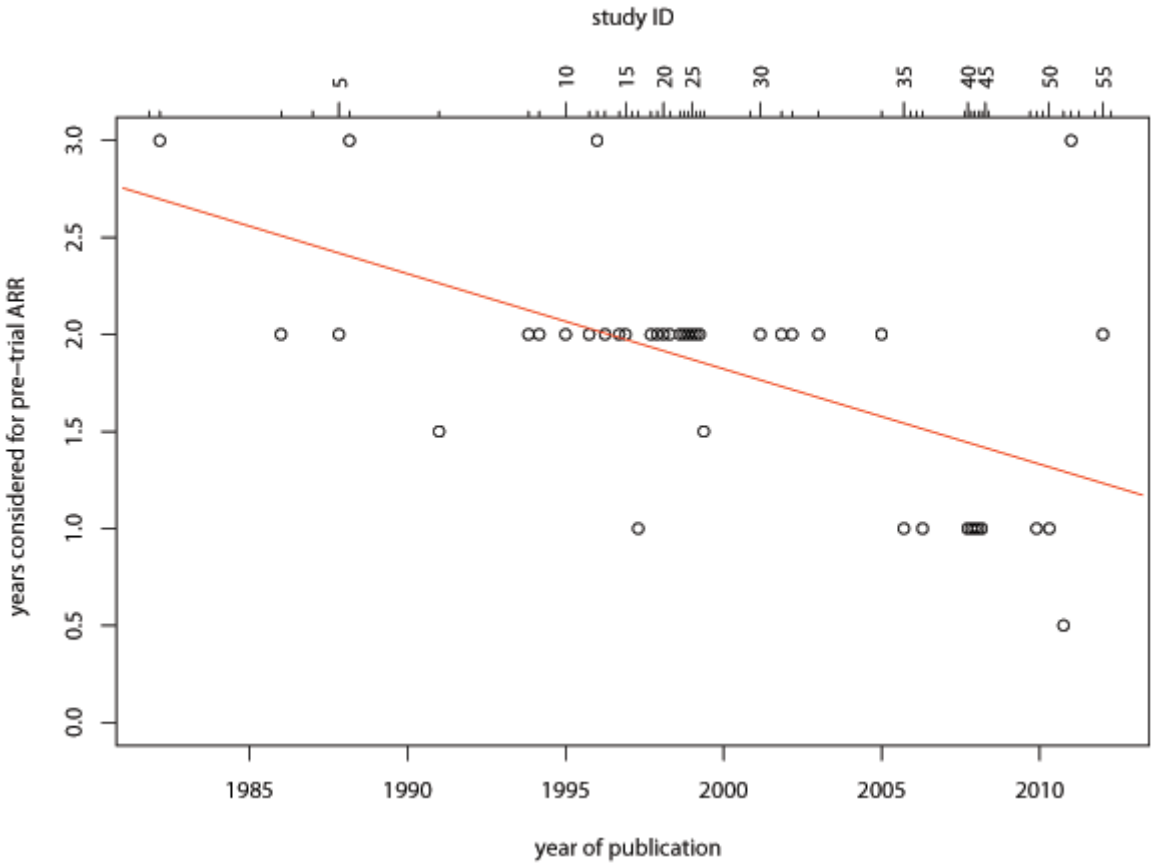

Figure 17: Number of years considered for the calculation of pre-trial ARR
The axis of abscissae represents time, the axis of ordinates the years considered when calculating the pre-trial ARR. The red trend line shows the result of the linear regression.

3.4.1.2 Eligible age

As Figure 18 shows, the minimum age for inclusion increased by one year every 29 years (p-value = 0.031; coeff = 0.035 (95% CI: 0.004 – 0.066)), while the maximum age for inclusion increased by one year every three years (p-value = 0.005; coeff = 0.364 (95% CI: 0.124 – 0.603)). With increasing limits of eligible age, an increase in baseline age becomes more likely.

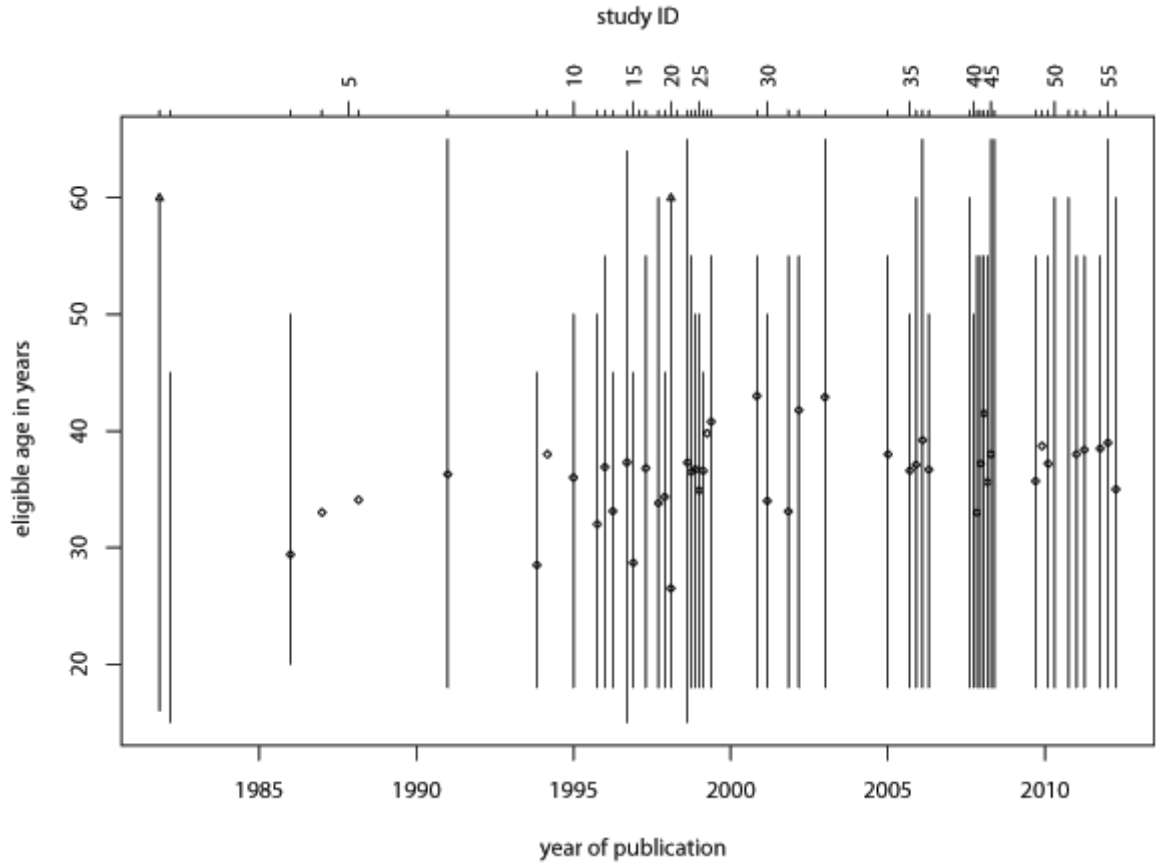

Figure 18: Eligible age
The axis of abscissae represents time, the axis of ordinates the age of patients. Bars depict the range of eligible age; checks indicate the factual mean age at baseline; arrows represent open ends.

3.4.1.3 Eligible scores on the EDSS

Neither the changes of the minimum (p-value = 0.051; coeff = -0.028 (95% CI: -0.056 – 0)) nor the maximum eligible score on the EDSS (p-value = 0.986; coeff < -0.001 (95% CI: -0.036 – 0.035)) were statistically significant. Figure 19 provides an overview of the margins of eligible EDSS scores over the years.

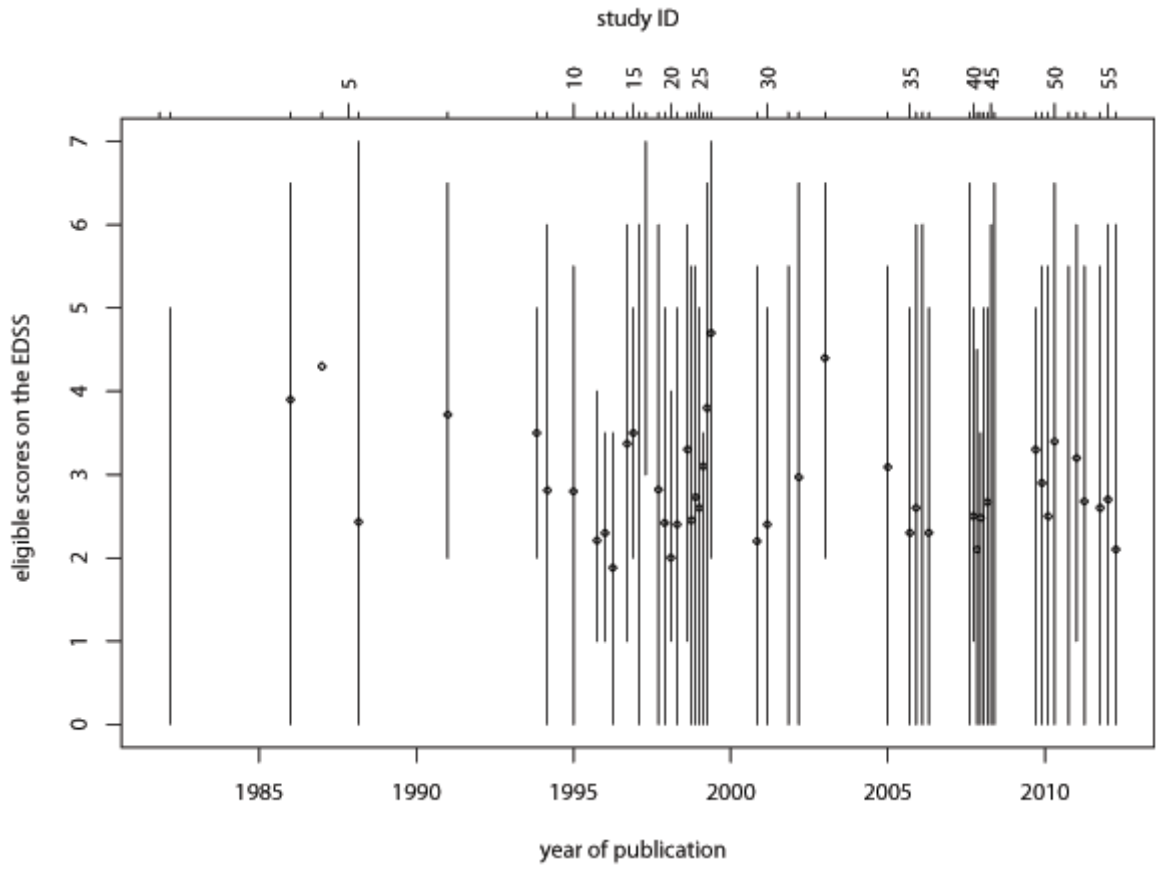

Figure 19: Eligible scores on the EDSS
The axis of abscissae represents time, the axis of ordinates scores on the EDSS. Bars depict the range of eligible age; checks indicate the factual mean age at baseline.

3.4.1.4 Minimum number of days without relapse

Changes in the minimum number of days before baseline without relapse did not reach statistical significance (p-value = 0.247; coeff = -0.623 (95% CI: -1.701 – 0.456)). Yet as visible in Figure 20, there seem to be some conventions as to how long patients must not have relapsed before baseline; the period of one month was most frequently stated.

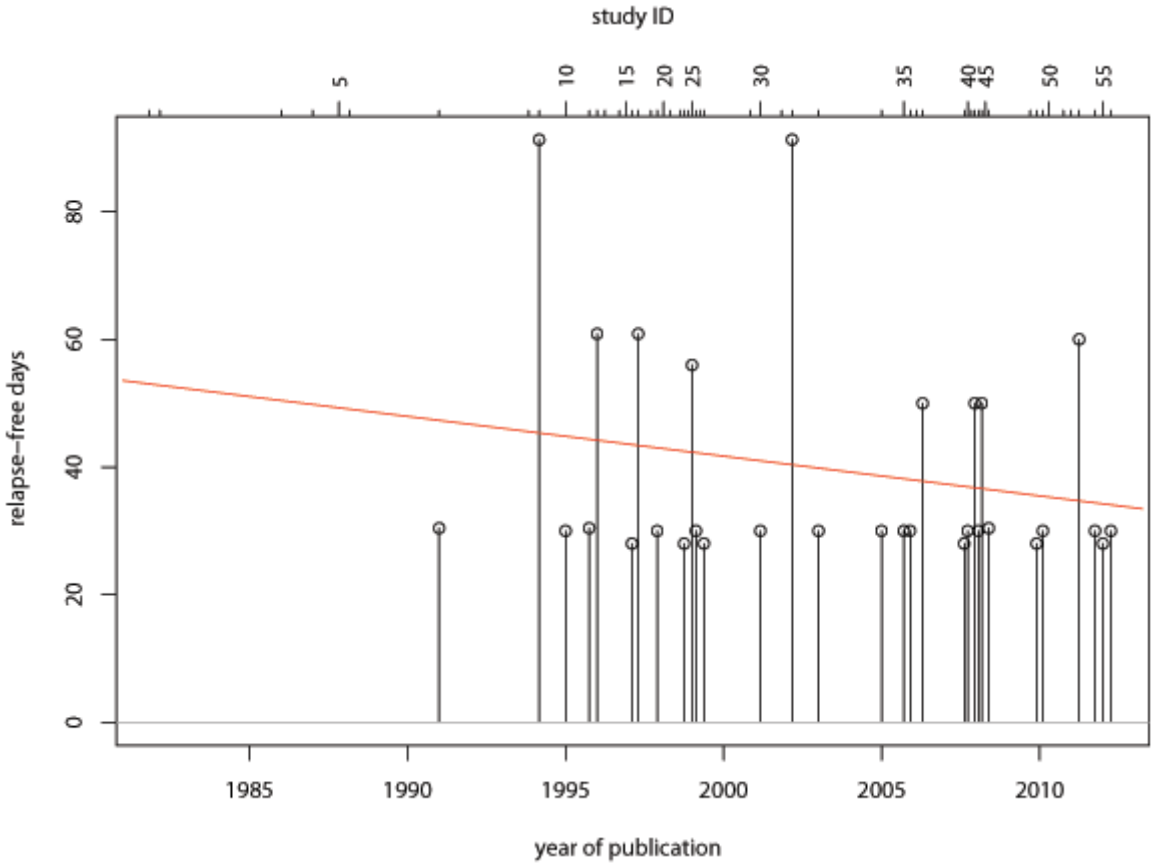

Figure 20: Minimum number of days without relapse
The axis of abscissae represents time, the axis of ordinates the minimum number of days without relapse. The red trend line shows the result of the linear regression.

3.4.1.5 Minimum number of days without the use of high-dose steroids

Changes in the minimum number of days before baseline without the use of high-dose steroids did not reach statistical significance (p-value = 0.059; coeff = -0.991 (95% CI: -2.019 – 0.038)). Similar to the minimum number of days without relapse (see Section 3.4.1.4), Figure 21 seems to show the existence of at least some conventions. The period of one month was most frequently stated.

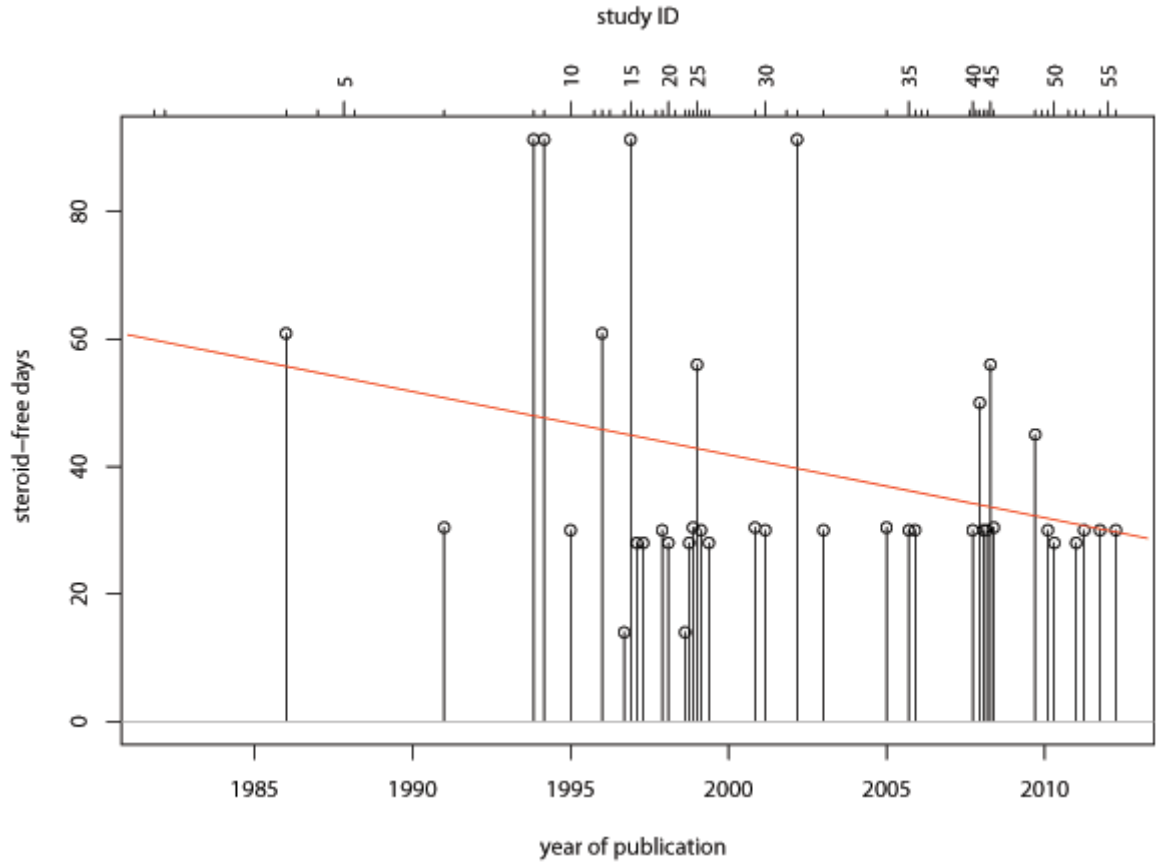

Figure 21: Minimum number of days without the use of high-dose steroids
The axis of abscissae represents time, the axis of ordinates the number of days without the use of high-dose steroids. The red trend line shows the result of the linear regression.

3.4.2 Additional study design features

Number of treatment arms

As shown in Figure 22, the average number of treatment arms increased by one treatment every 21 years ($p<0.001$; coeff = 0.048 (95% CI: 0.028 – 0.068)). The least number of treatment arms was two, as control groups were mandatory for the inclusion of trials to this study. As can be gathered from the tabulated summaries in the appendix, the additional treatment arms comprised only different dosages of the same intervention.

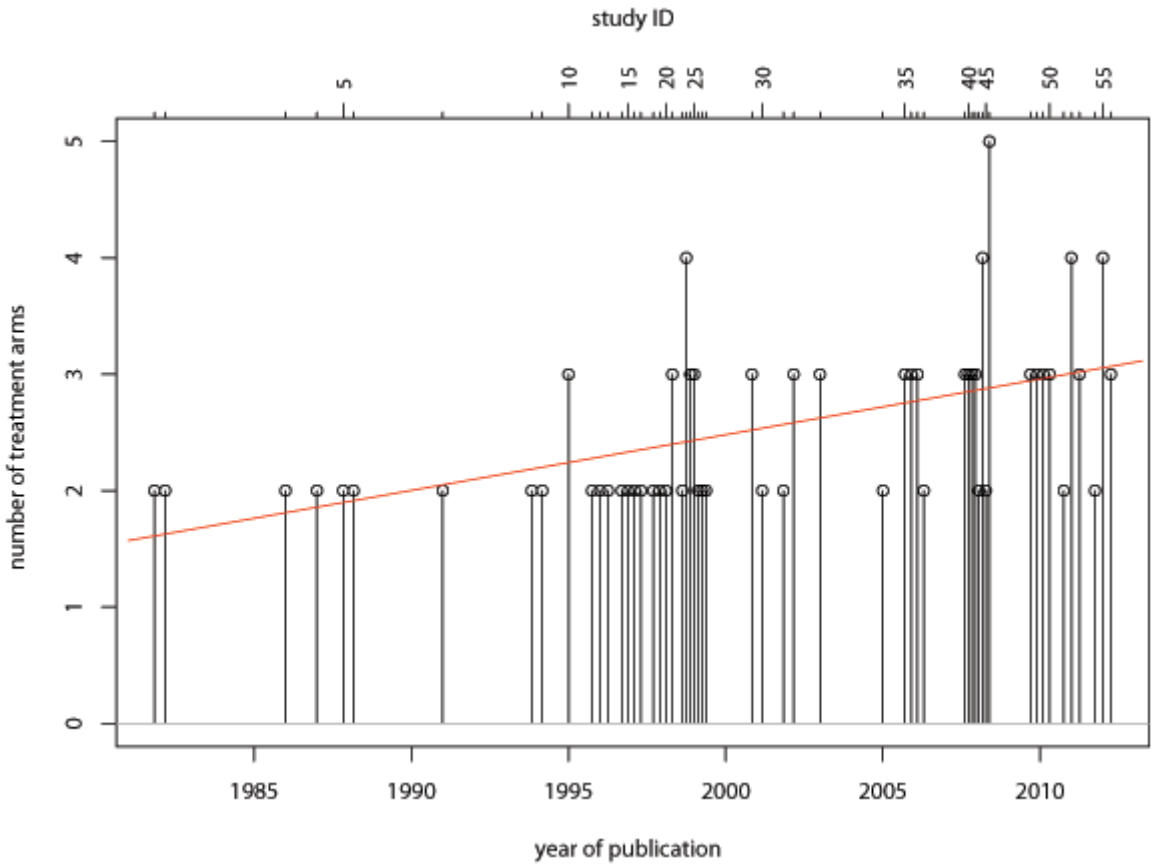

Figure 22: Number of treatment arms
The axis of abscissae represents time, the axis of ordinates the number of treatment arms. The red trend line shows the result of the linear regression.

Mean number of patients per treatment arm

The number of patients per treatment arm increased by 7 patients per year (p-value = 0.003; coeff = 7.028 (95% CI: 2.532 – 11.524)) on average. As becomes obvious in Figure 23, this finding is caused to a major part by six studies published after 2005.

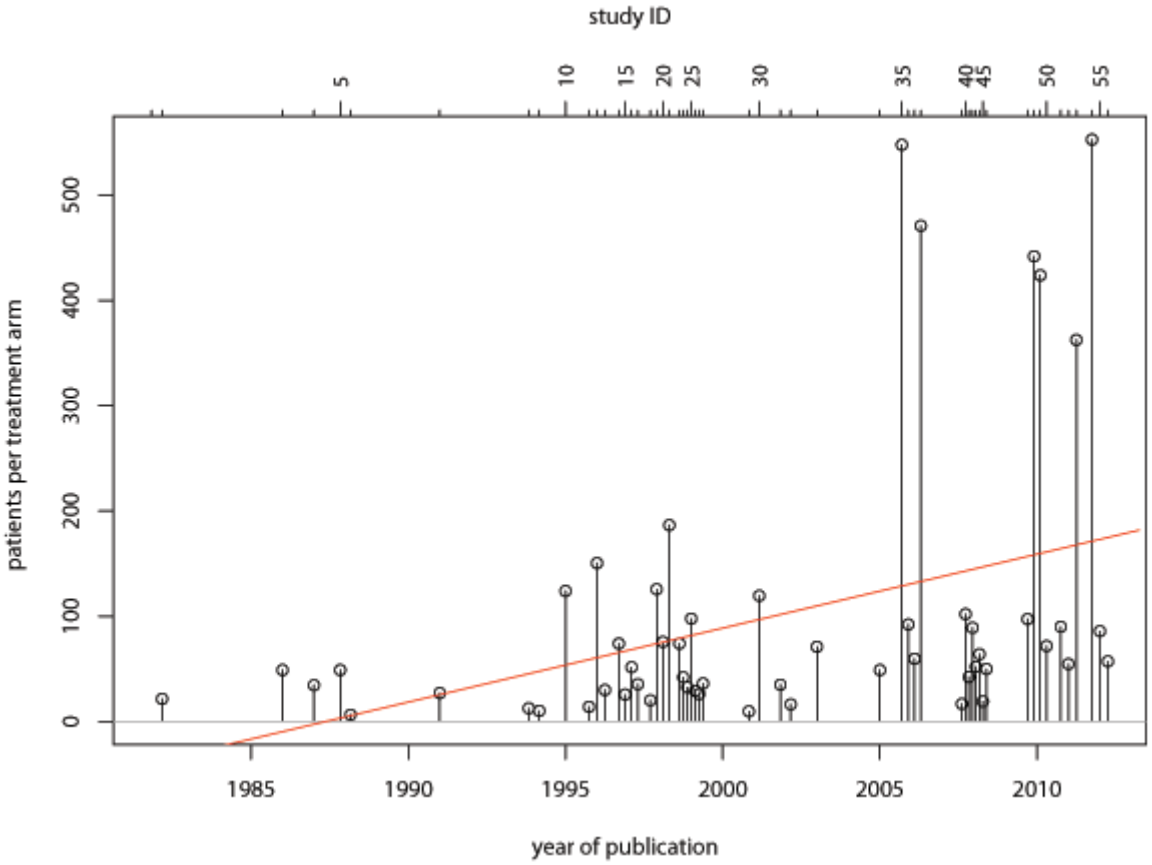

Figure 23: Number of patients per treatment arm
The axis of abscissae represents time, the axis of ordinates the number of patients per treatment arm. The red trend line shows the result of the linear regression.

3.5 Patient characteristics at baseline

3.5.1 Pre-trial ARRs

Placebo groups

Pre-trial ARRs in placebo groups decreased by 2.15% per year (95% CI: 1.49 – 2.82%), as shown in Figure 24. This approximates almost half of the analogous trend in trial ARRs. A direct comparison of both trends is part of the discussion.

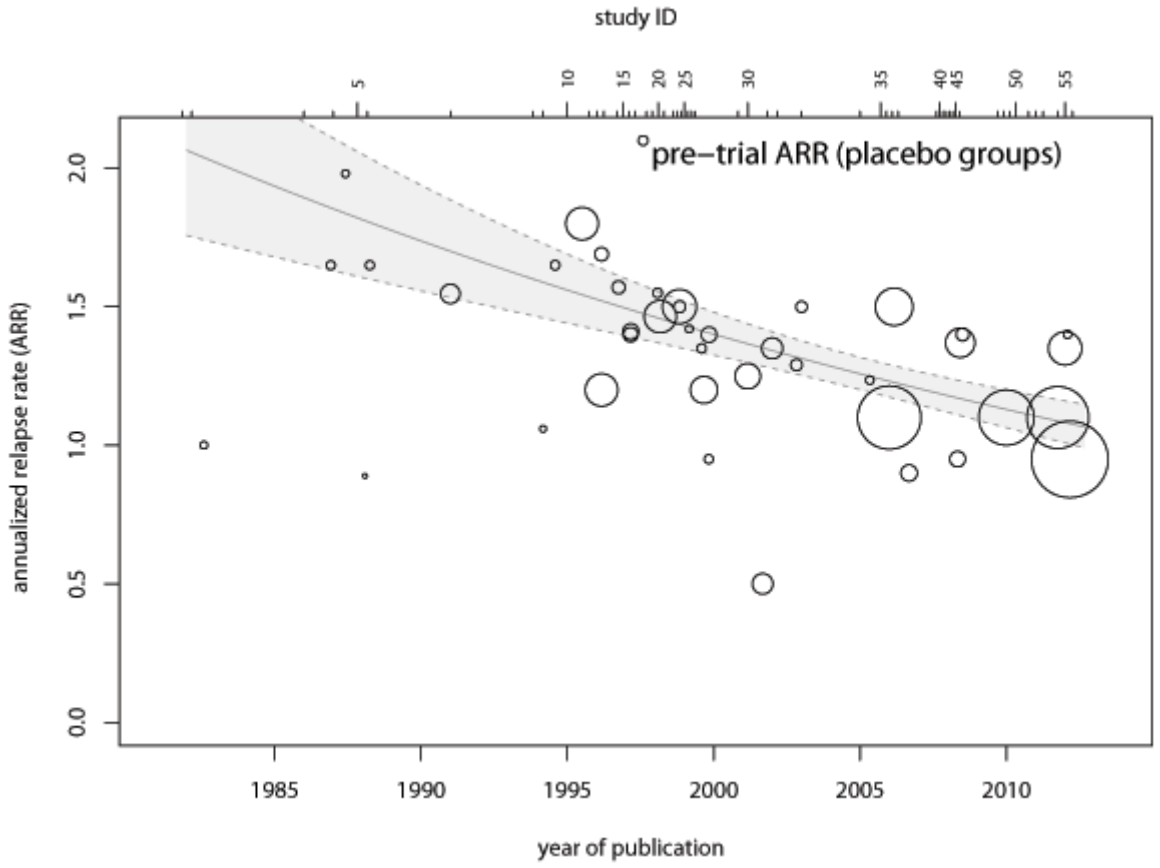

Figure 24: Pre-trial ARRs (placebo groups)
The axis of abscissae represents time, the axis of ordinates the pre-trial ARR. Symbol sizes correspond to SEs; the inner gray trend line shows the result of the regression; the outer dashed lines serve as borders to the 95% CI highlighted in light gray.

All groups

Pre-trial ARRs across all groups decreased by 1.98% per year (95% CI: 1.35 – 2.62%), as shown in Figure 25. The similarity to the finding in the placebo groups was to be expected.

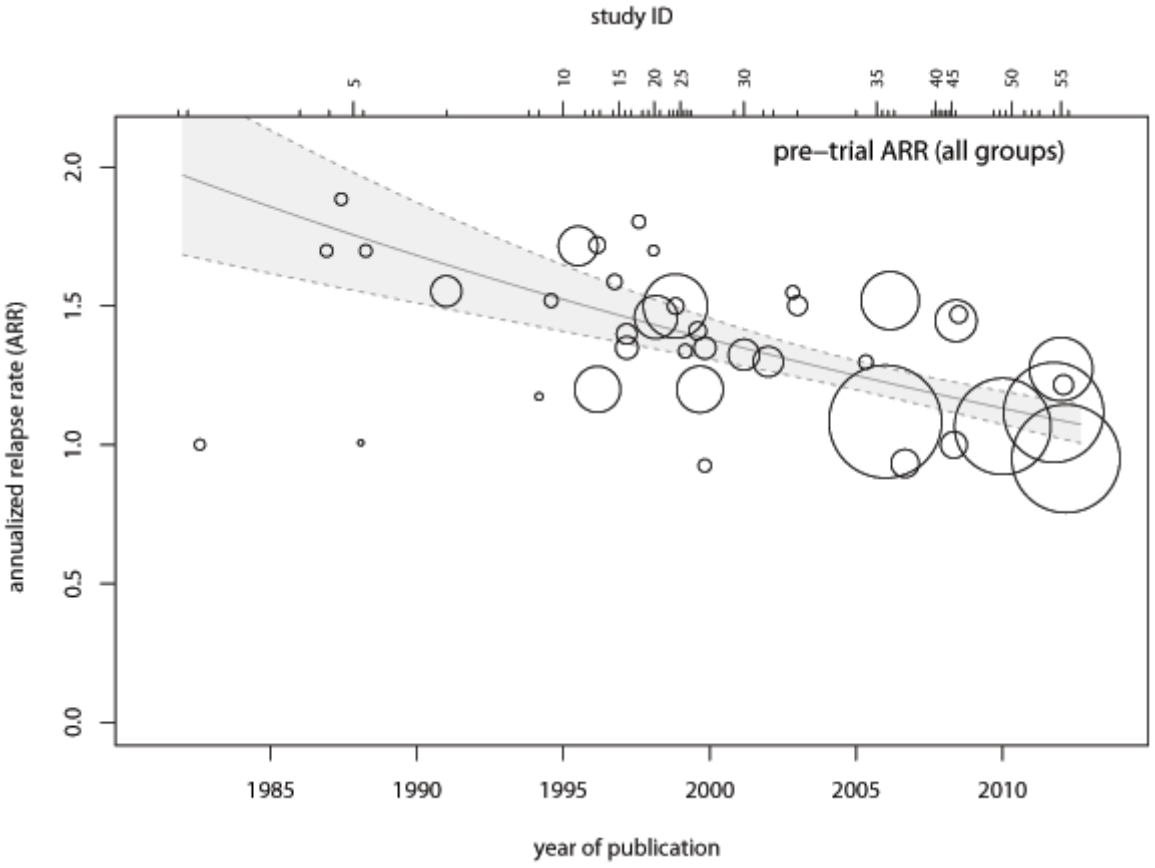

Figure 25: Pre-trial ARRs (all groups)
The axis of abscissae represents time, the axis of ordinates the pre-trial ARR. Symbol sizes correspond to SEs; the inner gray trend line shows the result of the regression; the outer dashed lines serve as borders to the 95% CI highlighted in light gray.

Multiple pre-trial ARRs of placebo groups

As shown in Table 2, six trials provided multiple pre-trial ARRs with corresponding SDs:

Table 2: Studies providing multiple pre-trial ARRs

Study	1st preceding year Mean (SD)	2nd preceding year Mean (SD)	Total Mean (SD)	n
Filippi 2006	1.5 (0.8)	0.7 (0.894)	1.1 (0.6)	548
Kappos 2010	1.5 (0.8)	0.7 (0.894)	1.1 (0.6)	418
O'Connor 2011	1.4 (0.7)	0.8 (0.714)	1.1 (0.5)	363
Miller 2012	1.7 (0.7)	1.0 (0.686)	1.35 (0.49)	99
Saida 2012	1.7 (1.6)	1.1 (2.538)	1.4 (1.5)	57
Comi 2012	1.3 (0.7)	0.6 (0.714)	0.95 (0.5)	363

ARRs of the year directly preceding baseline (including months -12 to -1) nearly doubled compared to those of the second preceding year before baseline (including months -24 to -13),

as shown in Figure 26 and Table 3. This stands in contrast to the notion of constant ARRs. A closer look at this finding is provided in the discussion.

Table 3: Meta-analysis of multiple pre-trial ARRs

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Filippi 2006	-0.7621401	0.05914688	20.3%	0.47 [0.42, 0.52]
Kappos 2010	-0.7621401	0.06772265	18.7%	0.47 [0.41, 0.53]
O'Connor 2011	-0.5596158	0.05370245	21.3%	0.57 [0.51, 0.63]
Miller 2012	-0.5306283	0.0803999	16.5%	0.59 [0.50, 0.69]
Saida 2012	-0.4353181	0.33002199	2.3%	0.65 [0.34, 1.24]
Comi 2012	-0.7731899	0.05540251	20.9%	0.46 [0.41, 0.51]
Total (95% CI)			**100.0%**	**0.51 [0.46, 0.56]**

Heterogeneity: Tau² = 0.01; Chi² = 15.24, df = 5 (P = 0.009); I² = 67%
Test for overall effect: Z = 13.07 (P < 0.00001)

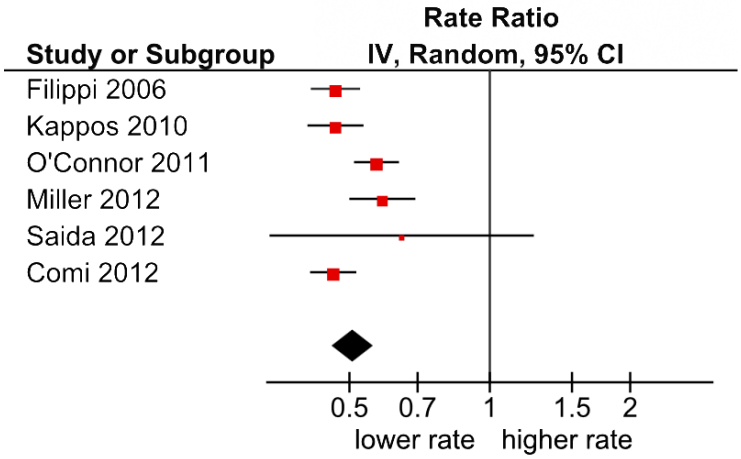

Figure 26: Forest-plot of multiple pre-trial ARRs

3.5.2 Age

Placebo groups

Mean age at baseline in placebo groups increased by one year every five years ($p<0.001$; coeff = 0.199 (95% CI: 0.098 – 0.299)) on average, as shown in Figure 27. This accumulates to an increase of six years in the investigated time span.

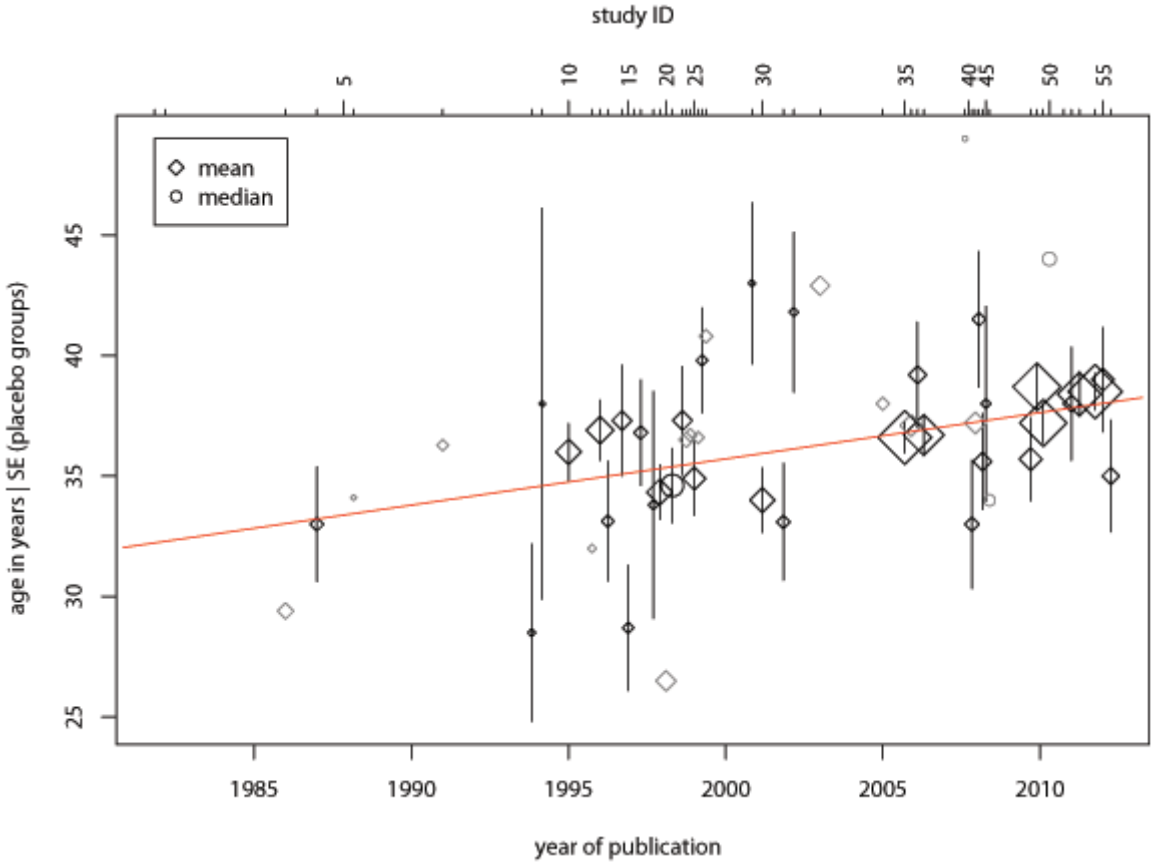

Figure 27: Mean age at baseline (placebo groups)
The axis of abscissae represents time, the axis of ordinates the age of patients. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

All groups

As shown in Figure 28, mean age at baseline across all groups increased by one year every five years ($p<0.001$; coeff = 0.2 (95% CI: 0.111 – 0.288)) on average, very similar to the finding in the placebo patients. A closer look at this change in the composition of trial populations will be part of the discussion.

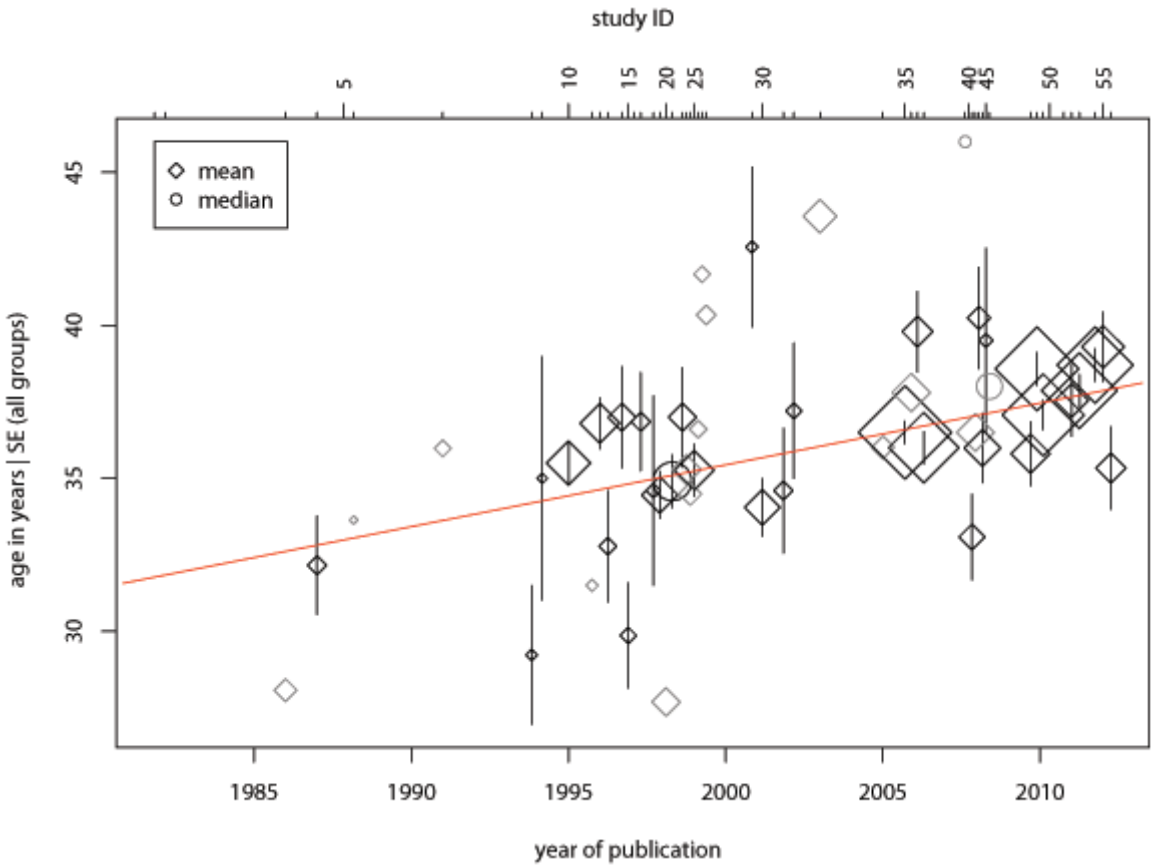

Figure 28: Mean age at baseline (all groups)
The axis of abscissae represents time, the axis of ordinates the age of patients. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

3.5.3 Disease duration

Placebo groups

Mean disease duration in placebo groups increased one year every eight years (p-value = 0.048; coeff = 0.122 (95% CI: 0.001 – 0.243)) on average, as shown in Figure 29. The average patient's history of MS before commencement of the trial was therefore prolonged by nearly four years in the time span investigated.

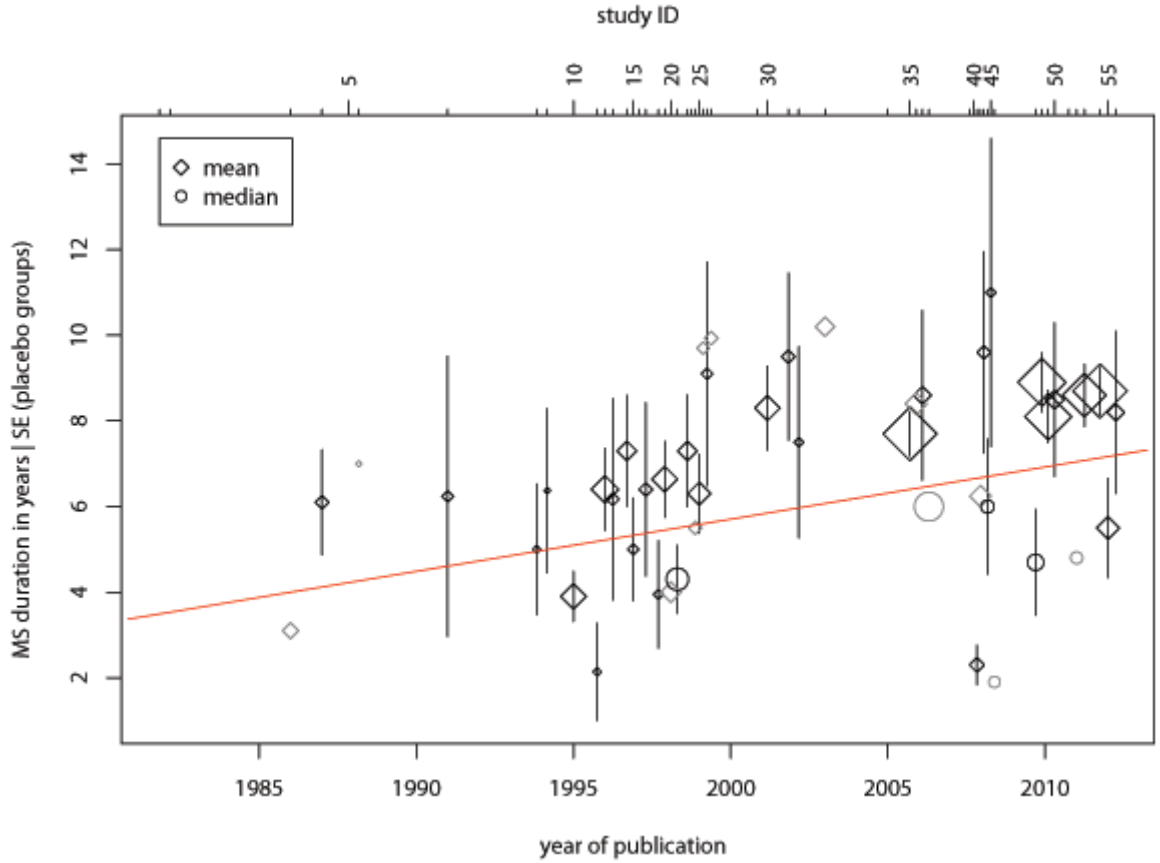

Figure 29: Mean disease duration at baseline (placebo groups)
The axis of abscissae represents time, the axis of ordinates the duration of disease. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

All groups

As shown in Figure 30, the mean disease duration across all groups increased one year every eight years (p-value = 0.042; coeff = 0.119 (95% CI: 0.005 – 0.233)) on average. The similarity to the finding in the placebo groups was expected.

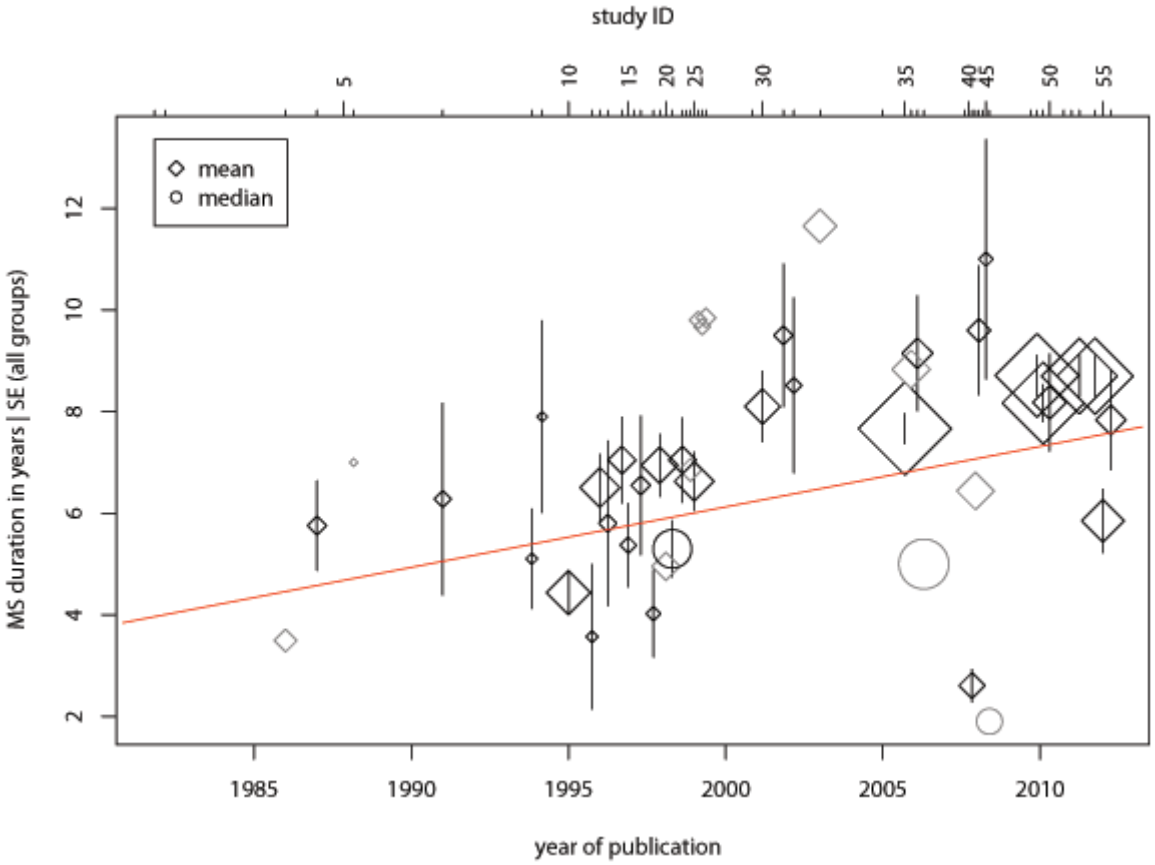

Figure 30: Mean disease duration at baseline (all groups)
The axis of abscissae represents time, the axis of ordinates the duration of disease. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

3.5.4 Scores on the EDSS

Placebo groups

Changes in mean scores on the EDSS in placebo groups did not reach statistical significance (p-value = 0.289; coeff = 0.011 (95% CI: -0.01 – 0.031)), as visible in Figure 31. The red trend line in Figure 31 - although insignificant - may appear counterintuitive, however, a look the results of the corresponding epoch analysis and the frames of standard errors especially serves as an explanation for this phenomenon.

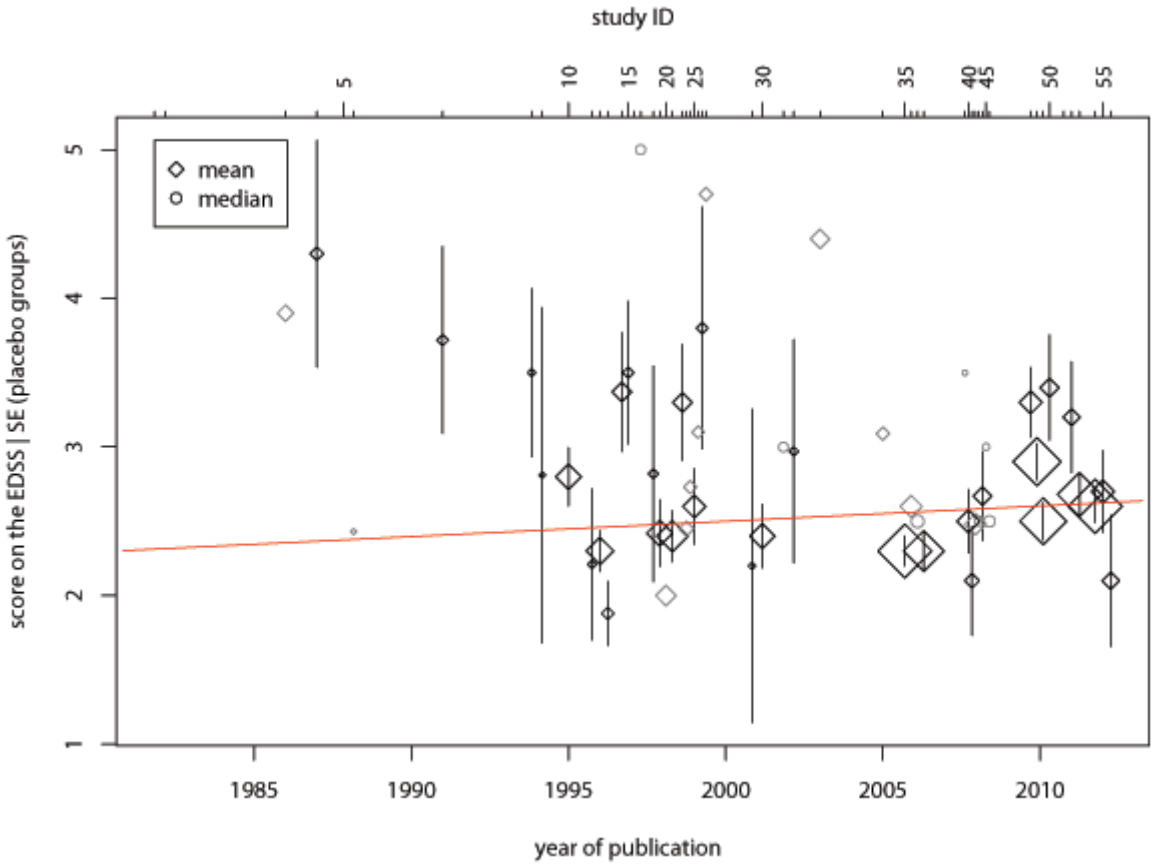

Figure 31: Mean scores on the EDSS (placebo groups)
The axis of abscissae represents time, the axis of ordinates scores on the EDSS. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

All groups

Changes in mean scores on the EDSS across all groups did not reach statistical significance (p-value = 0.554; coeff = 0.007 (95% CI: -0.017 – 0.03)), as visible in Figure 32. The similarity to the finding in the placebo groups was expected.

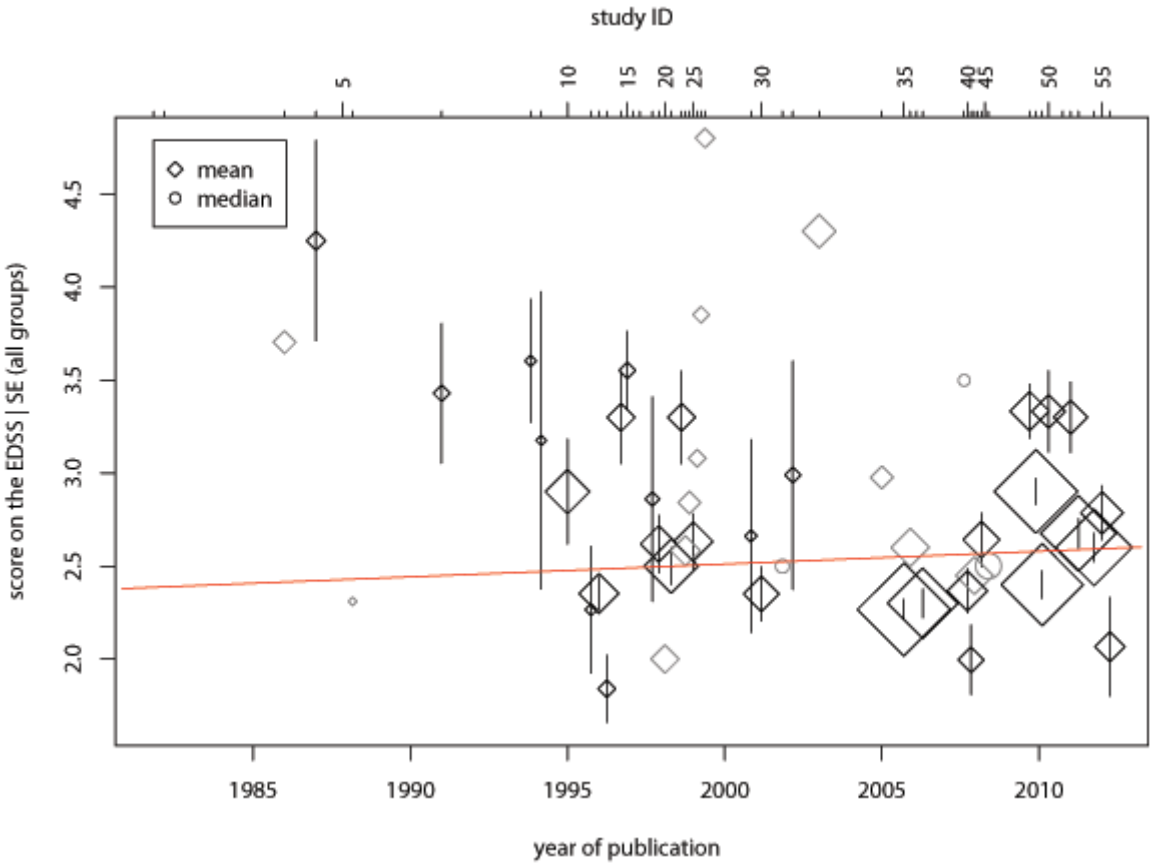

Figure 32: Mean scores on the EDSS (all groups)
The axis of abscissae represents time, the axis of ordinates scores on the EDSS. The red trend line shows the result of the linear regression; gray symbols indicate values omitted due to lacking SEs; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

3.5.5 Gender distribution

Placebo groups

Changes in the proportion of women among placebo patients at baseline did not reach statistical significance (p-value = 0.337; coeff = -0.001 (95% CI: -0.004 – 0.001)), as depicted in Figure 33. This finding was rather unexpected; the discussion will delve into this point.

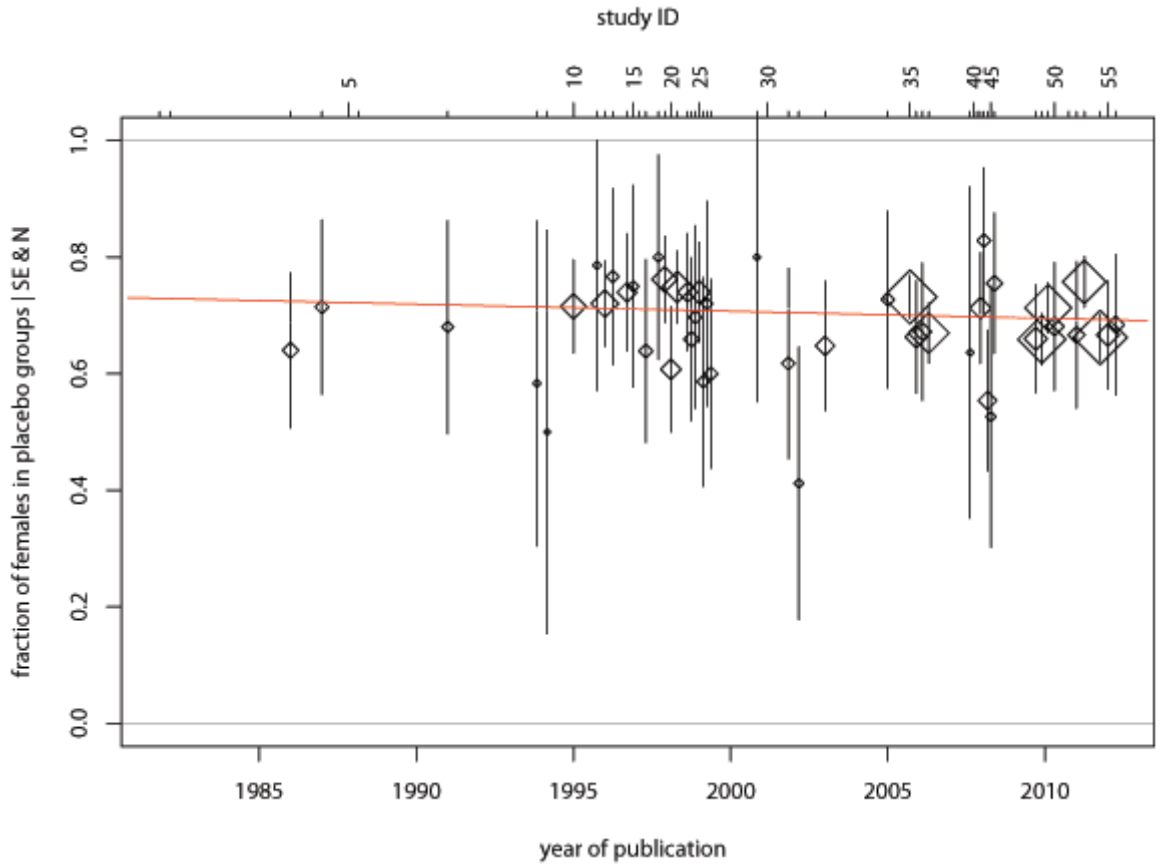

Figure 33: Changes in the fraction of female patients (placebo groups)
The axis of abscissae represents time, the axis of ordinates the fraction of female patients. The red trend line shows the result of the linear regression; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

All groups

Changes in the proportion of women among patients across all groups at baseline did not reach statistical significance (p-value = 0.593; coeff = -0.001 (95% CI: -0.002 – 0.001)), as depicted in Figure 34. The similarity to the finding in the placebo groups was expected.

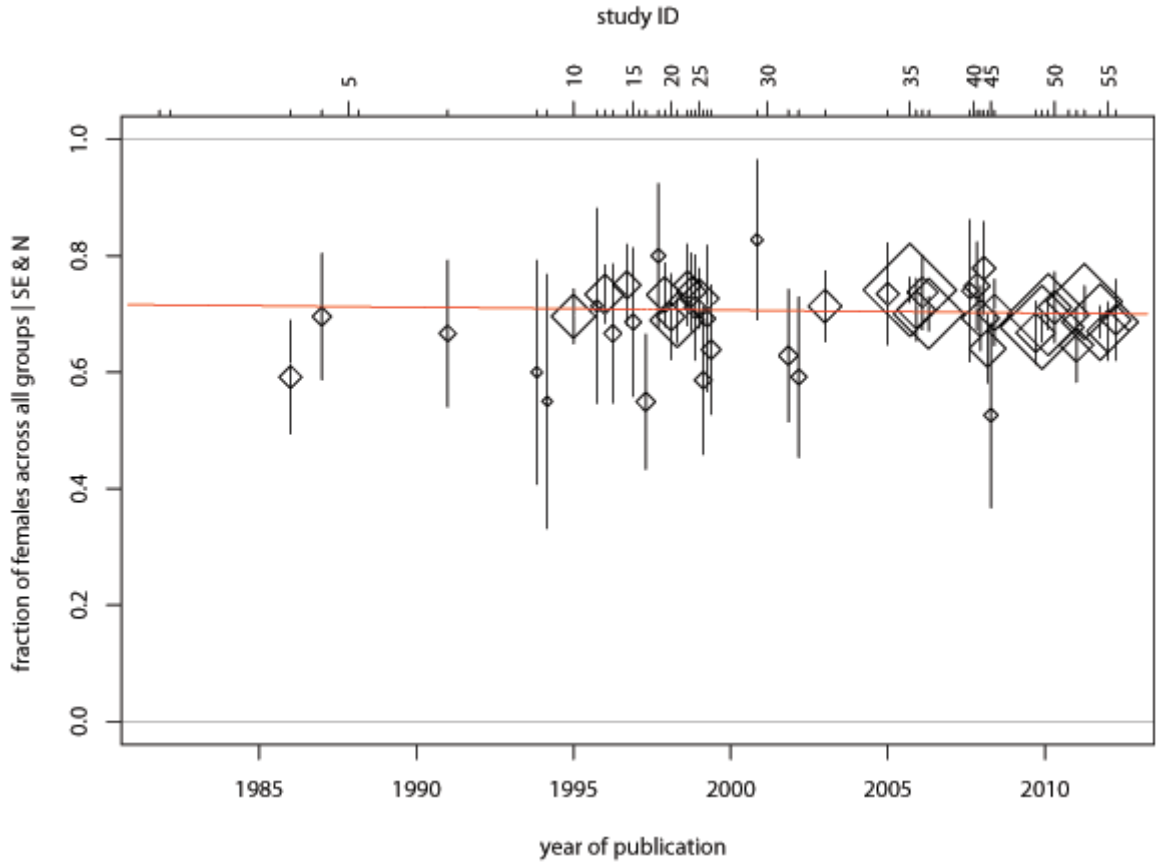

Figure 34: Changes in the fraction of female patients (all groups)
The axis of abscissae represents time, the axis of ordinates the fraction of female patients. The red trend line shows the result of the linear regression; whiskers indicate the 95% CI; symbol size correlates to the square root of sample size (compare 10.2.).

3.6 Epoch analyses

Table 4 gives an overview of the results of the epoch analyses. Mean values of the different clusters are stated with corresponding SEs and were tested for equality across epochs (p-values). Statistically significant findings are shown in red.

Table 4: Results of the epoch analyses

Item	p -value		1982 – 1994	1995 – 2000	2001 – 2009	2010 - 2012
trial ARR in placebo groups	<0.001	mean	1.155	1.078	0.767	0.412
		SE	0.373	0.071	0.116	0.032
duration of placebo-controlled follow-up (in days)	0.004	mean	557.882	657.57	275.594	405.288
		SE	104.147	71.679	73.643	98.803
scores on the OQS	0.291	mean	4	4.421	4.444	4.6
		SE	0.233	0.161	0.165	0.221
number of eligibility criteria	0.004	mean	8.889	13.79	18.889	27.3
		SE	3.785	2.605	2.677	3.591
number of words describing the eligibility criteria	0.002	mean	81.556	125.9	158.111	253.4
		SE	32.101	22.094	22.699	30.454
number of characters describing the eligibility criteria	0.002	mean	459.111	711.526	894.333	1486.4
		SE	190.731	131.27	134.867	180.944
minimum pre-trial ARR for inclusion	0.824	mean	1	1	0.964	1.074
		SE	0.103	0.064	0.073	0.09
number of years considered for the calculation of pre-trial ARRs	0.008	mean	2.214	1.972	1.417	1.5
		SE	0.204	0.127	0.156	0.242
minimal score on the EDSS for inclusion	0.107	mean	0.667	0.632	0.167	0.1
		SE	0.293	0.164	0.169	0.227
maximal score on the EDSS for inclusion	0.269	mean	6	5.237	5.472	5.7
		SE	0.364	0.205	0.21	0.282
minimum number of days without relapse	0.342	mean	60.873	38.219	39.211	34.333
		SE	12.493	5.587	4.9	7.213
minimum number of days without the use of high-dose steroids	0.02	mean	68.484	35.473	38.356	31.571
		SE	9.469	5.061	5.252	7.158
mean age in placebo groups at baseline	0.004	mean	32.031	35.382	36.532	37.977
		SE	2.267	0.622	0.5	0.459
mean age across all groups at baseline	<0.001	mean	31.553	35.33	36.329	37.836
		SE	1.961	0.547	0.408	0.373
mean disease duration in placebo groups at baseline	0.007	mean	5.836	5.154	5.453	8.146
		SE	1.733	0.608	0.635	0.609
mean disease duration across all groups at baseline	0.01	mean	5.779	5.7	5.943	8.287
		SE	1.717	0.596	0.579	0.527
mean score on the EDSS in placebo groups at baseline	0.004	mean	3.671	2.474	2.347	2.725
		SE	0.475	0.098	0.091	0.076
mean score on the EDSS across all groups at baseline	0.003	mean	3.619	2.562	2.309	2.722
		SE	0.497	0.112	0.086	0.077
mean pre-trial ARR in placebo groups	0.001	mean	1.571	1.466	1.202	1.058
		SE	0.255	0.077	0.067	0.051
mean pre-trial ARR across all groups	<0.001	mean	1.569	1.424	1.219	1.067
		SE	0.218	0.067	0.056	0.042
gender distribution in placebo groups	0.34	mean	0.657	0.721	0.7	0.692
		SE	0.048	0.015	0.014	0.012
gender distribution across all groups	0.031	mean	0.635	0.71	0.718	0.692
		SE	0.036	0.01	0.008	0.007

3.7 Meta-regression of statistically significant temporal trends

The temporal trend line for the trial ARR, as shown in Figure 6, explains about 46% of the variation observed in trial ARRs over the years (Figure 35, left column). To gain insights into the drivers of this trend, meta-regression incorporating changes in patient populations and trial characteristics was utilized. After taking all possible combinations of variables into consideration, the final model included pre-trial ARR, the number of years considered for the calculation of pre-trial ARR, duration of placebo-controlled follow-up and mean MS duration at baseline, as shown in Figure 35. The year of publication was added for comparison with the simple model including the time trend only. In the resulting model explaining about 69% of the variation in trial ARR, the temporal trend becomes insignificant with major contributors being pre-trial ARR, the number of years used to calculate pre-trial ARR, study duration, and MS duration (Figure 35, right column).

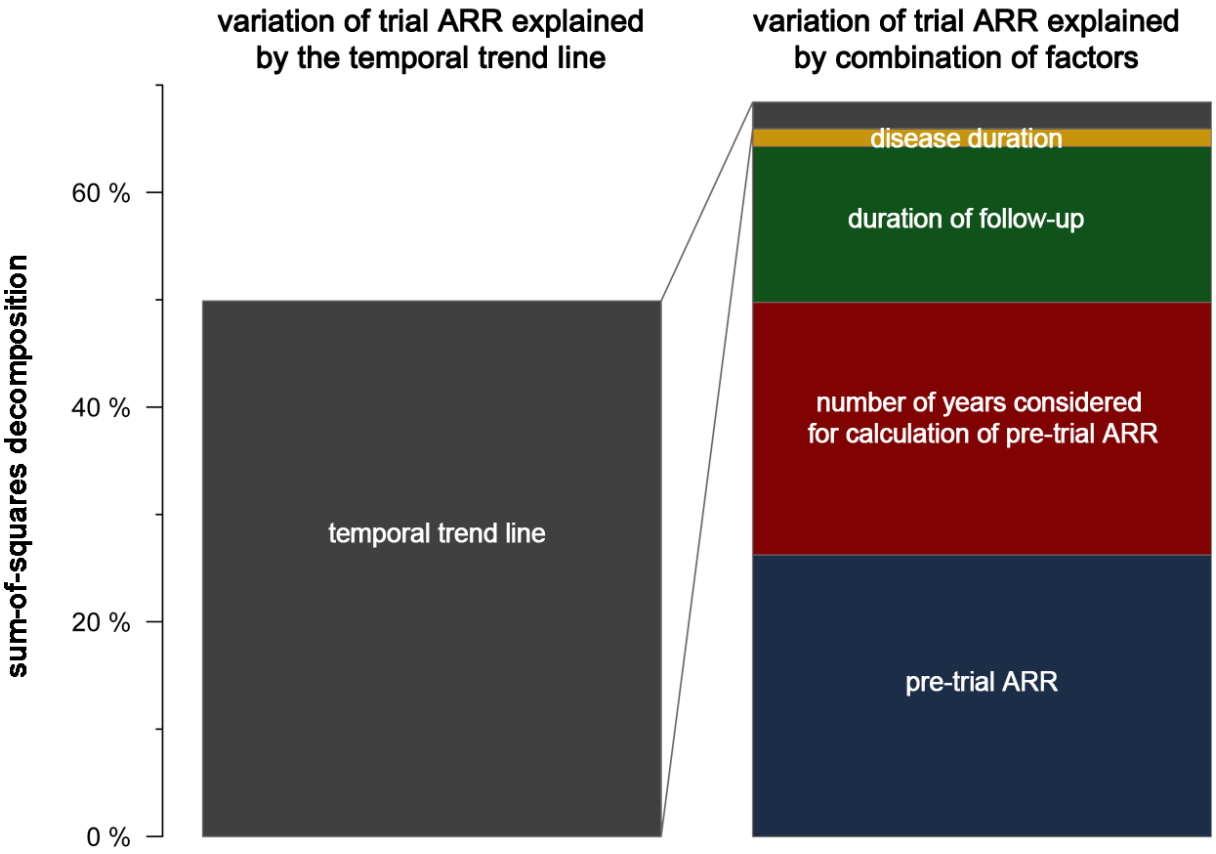

Figure 35: Meta-regression explaining variation of trial ARR
The left column shows the percentage of variation in trial ARRs that can be explained by the temporal trend line shown in Figure 6; the right column shows the percentage of variation in trial ARRs that can be explained by the named factors: the temporal trend line becomes a minor contributor.

4 Discussion

The data which this dissertation was based on were extracted from published journals, thus bearing editorial restrictions, as journals can only afford for the most substantial data to be published as opposed to the entire data. Hence, in most cases only aggregated data was accessible, not individual patient data, which would have been of higher statistical value. Still, Quality and quantity of reported data varied widely, as depicted in the increase in scores on the OQS (see Section 3.3) and in sample size. This may reflect higher trial quality or better reporting in more recent trials, consistent with the findings of Signori [Signori et al. 2012].

Results of the epoch analyses have to be interpreted with caution, since the clusters were defined arbitrarily. In addition, mean values of the first cluster in particular are based on small samples, making aberrancies in this epoch more likely. One example of this is the detected drop in the minimum steroid-free time before baseline since 1995, based only on four trials in the first cluster.

Nonetheless, the available data proved conclusive with respect to the aim of this dissertation, namely describing the downward trend in trial ARRs in placebo patients and identifying possible causal factors.

In the 56 RCTs analyzed in this dissertation, the trial ARRs in placebo patients decreased by 4.56% per year (95% CI: 3.24 – 5.89%). This is consistent with previous findings by Inusah et al. and Nicholas et al., who conducted their reviews on different, though overlapping sets of trials: Nicholas et al. found trial ARRs to be decreasing at 6.2% per year (95% CI: 4.2 – 8.1%) in a set of 26 RCTs [Nicholas et al. 2011a], Inusah stated absolute data and found a yearly reduction of 0.036 (95% CI: 0.02 – 0.052) relapses in 32 RCTs [Inusah et al. 2010].

Also, pre-trial ARRs were found to be decreasing by 2.15% per year (95% CI: 1.49 – 2.82%). The causal relationship between pre-trial and trial ARR is obvious: If patients have a lower ARR at the start of a study, lower outcomes (= trial ARRs) are to be expected. Figure 36 captures the development of both rates over time.

Decreasing pre-trial ARRs may in turn be related to the increasing age and duration of MS of patients in the trials.

Tremlett et al. found a reduction in ARRs by 17% for every 5 years of MS duration [Tremlett et al. 2008]. The increase in MS duration by 3.6 years, as observed in this study (see Section 3.5.3), could constitute a 13% decrease in ARRs. Similarly, patients at baseline were on average approximately six years older at the end of the observation period than at its beginning (see Section 3.5.2) – this notion is consistent with the accordingly increasing limits of eligible age (see Section 3.4.1.2). A correlation of higher age with lower trial ARR could be shown in a meta-analysis of 13 patient cohorts [Stellmann et al. 2012]. Considering this, in an older trial population with longer disease duration, a decrease in pre-trial ARR is not surprising.

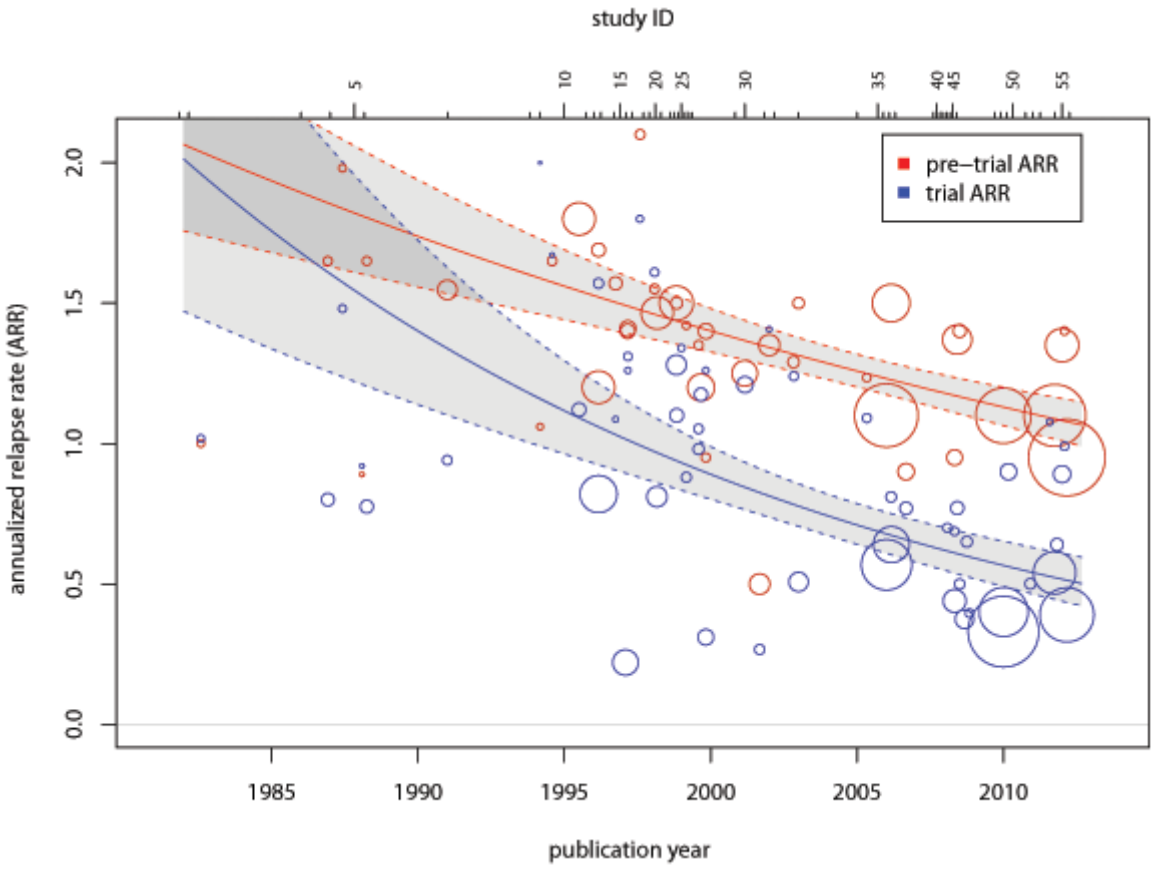

Figure 36: Pre-trial ARR and trial ARR in placebo groups
The axis of abscissae represents time, the axis of ordinates the ARRs of placebo patients. Symbol sizes correspond to SEs; inner trend lines show the results of regressions; outer dashed lines serve as borders to the 95% CIs highlighted in light gray.

Older patients in newer trials with longer disease duration but relatively stable EDSS scores (after an early drop, especially in trials since 1995; see Section 3.6) may even have less severe disease courses than the younger patients in older trials. The increasing availability of increasingly effective disease modifying treatments could be a likely driver in this, as suggested by Inusah [Inusah et al. 2010].

Another factor contributing to the decrease in trial ARRs is the reduced time period over which pre-trial ARRs had been calculated: this decreased on average by 1.5 years over the past three decades (see Section 3.4.1.1). Using shorter periods of time over which pre-trial ARRs are calculated, might thereby allow trials to include patients who, if pre-trial ARR was assessed over a longer time span, might not have been eligible for trial inclusion. In fact, this effect can be witnessed in two of the trials that provided multiple pre-trial ARRs (study IDs #36 and #54): Both trials presented average pre-trial ARRs for the two-year period before baseline that would not have been eligible for inclusion, but were included for their pre-trial ARRs assessed for the one-year period before baseline.

The shortening of the time period considered for the estimation of the pre-trial ARR could be a principal factor driving the regression to the mean effect, which has previously been described by Martínez-Yélamos [Martínez-Yélamos et al. 2006] and Nicholas [Nicholas et al. 2012] and

is very evident in the latest publications on the AFFIRM and the TOP studies [Kappos et al. 2013].

The notion that patients are recruited into a study shortly after a flare up of disease activity is supported by the finding that the meta-analysis of multiple pre-trial ARRs of the same patients in the second preceding year before baseline is almost half of the ARR in the year directly before baseline (see Section 3.5.1).

Since the relative incidence of MS in women compared to men has risen from 2:1 to 4:1 over recent years [Koch-Henriksen and Sørensen 2010] and a positive correlation between trial ARR and female sex was shown by Held [Held et al. 2005], the lack of a temporal trend over the 30 year observation period in the gender ratio (see Section 3.5.5) was unexpected, as it would have served as one explanation for the phenomenon in question. The epoch analysis (see Section 3.6) even indicates a decrease of female patients across all groups since 1995, although this militates against the gender ratio playing a role in the downward trend in trial ARRs.

While growing numbers of eligibility criteria reflect the increasing understanding of the complexity of possible influences on outcome variables such as the trial ARR, early trials with fewer eligibility criteria might have been more susceptible to such influences than modern ones.

Similarly, ever changing definitions of MS and relapses, as well as varying forms of report, confirmation and treatment in case of relapses undoubtedly play a role, as has been suggested by Inusah [Inusah et al. 2010].

To find indications of not only higher quantity, but also higher complexity in eligibility criteria, analyses of words and characters per criterion were carried out, but did not demonstrate signs of increasing complexity.

Also, the growing numbers of eligibility criteria (see Section 3.4.1) did not seem to have an impact on the heterogeneity of the patients, since no incremental underdispersion (a ratio of variance to the mean below 1) in trial ARRs was detectable (see Section 3.2.4), which would have been a sign of increasing homogeneity of placebo groups.

As secondary findings, the average number of treatment arms as well as the average number of patients in treatment arms increased (see Section 3.4.2) over time.

The duration of placebo-controlled follow-up decreased over time – although this trend is likely caused by the inclusion of both phase II and phase III trials in the analysis, the former being relatively short as a matter of principle [European Medicines Agency 1998] and should be interpreted with caution.

In the essential meta-regression (see Section 3.7) the temporal trend line became relatively insignificant in explaining the variation in trial ARRs, when the pre-trial ARR, the number of years considered for the calculation of pre-trial ARR, the duration of placebo-controlled follow-up and the mean MS duration at baseline were included in the calculation. This combination of variables was able to explain as much as 69% of the variation in trial ARRs, the most important variable being the pre-trial ARR, the duration of placebo-controlled follow-up being less important.

Future comparisons of therapies that have been used in trials conducted at different points in time should consider the covariates described above in their interpretation of potential differences. With more agents becoming available for the treatment of MS, this is an issue of increasing importance.

5 Summary

Recent studies have shown a decrease in annualized relapse rates (ARRs) in placebo groups of randomized controlled trials (RCTs) in relapsing multiple sclerosis (RMS). This dissertation aimed to describe this trend in a different set of RCTs and to investigate whether patient baseline characteristics, eligibility criteria and other study design features could explain this phenomenon.

A literature search of randomized, placebo-controlled trials in RMS offering data on relapses in placebo groups identified 56 suitable trials. Data on eligibility criteria and baseline characteristics were extracted and tested for significant trends over time.

Several temporal trends were identified: The number of years considered for the calculation of pre-trial ARR as well as pre-trial ARRs themselves decreased, as did the duration of placebo-controlled follow-up. Pre-trial ARRs of the first and second preceding year before baseline showed major inconsistencies. Limits of eligible age as well as mean age increased, as did the mean disease duration, the number of eligibility criteria and the number of words and characters describing them, scores on the OQS, the number of treatment arms and the average number of patients per treatment arm.

A meta-regression was conducted to estimate the contribution of these temporal trends to the decrease of trial ARRs over time. In the final meta-regression modeling of the trial placebo ARR, the date of publication was found to be insignificant in explaining the variation in trial placebo ARR, whereas pre-trial ARR, the number of years used to calculate pre-trial ARR, disease duration and the duration of follow-up became major contributors.

In conclusion, the decline in trial ARRs most likely results from decreasing pre-trial ARRs and a shorter time period over which these were calculated. Increasing duration of illness may also contribute to the phenomenon.

6 List of Abbreviations

ARR ..... Annualized Relapse Rate
CHMP ..... Committee For Medicinal Products For Human Use
CI ..... Confidence interval
CIS ..... Clinically Isolated Syndrome
CNS ..... Central nervous system
coeff ..... Coefficient
d ..... Day
DOI ..... Digital object identifier
ECTRIMS ..... European Committee for Treatment and Research in Multiple Sclerosis
EDSS ..... Expanded Disability Status Scale
et al. ..... Latin: et alii ≈ and others
FRCP ..... Fellow of the Royal College of Physicians
ID ..... Identification
i.e. ..... Latin: id est ≈ that is
i.m. ..... Intramuscularly
i.v. ..... Intravenously
IVIg ..... Intravenous Immunoglobulin
(r)IFN ..... (Recombinant) Interferon
(M)IRU ..... (1,000,000) Interferon Reference Unit(s)
(M)IU ..... (1,000,000) International Unit(s)
IQR ..... Interquartile range
MRI ..... Magnetic resonance imaging
MS ..... Multiple sclerosis
MSFC ..... Multiple Sclerosis Functional Composite
MSSS ..... Multiple Sclerosis Severity Score
MSTCG ..... Multiple Sclerosis Therapy Consensus Group
No. ..... Latin: numero ≈ number
OQS ..... Oxford Quality Scale
p ..... Page
PPMS ..... Primary-progressive multiple sclerosis
PRMS ..... Progressive-relapsing multiple sclerosis
RCT ..... Randomized controlled trial
RMS ..... Relapsing multiple sclerosis
RRMS ..... Relapsing-remitting multiple sclerosis
s.c. ..... Subcutaneously
SD ..... Standard deviation
SE ..... Standard error
SPMS ..... Secondary-progressive multiple sclerosis
URL ..... Uniform resource locator
w ..... Week

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10 Appendix

10.1 Poster P1022 for ECTRIMS [Steinvorth et al. 2012]

GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

Time trends in baseline characteristics and eligibility criteria in trials in relapsing multiple sclerosis

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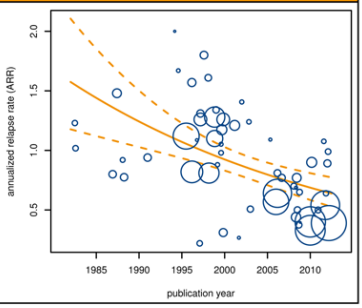
THE PROBLEM

Recent studies (Nicholas et al.[1], Inusah et al. [2]) detected **a decrease in annualized relapse rates (ARRs) in placebo groups in randomized controlled trials (RCTs)** in relapsing multiple sclerosis (RMS), that to our knowledge lacks sufficient explanation and questions inter-trial comparability. We investigated this trend systematically to explore whether patient baseline characteristics and eligibility criteria of RCTs in RMS are implicated in this phenomenon.
Therefore, we conducted a **systematic literature search** for RCTs in RMS providing ARR data. In 56 studies eligible for our review, covering the time from 1982 to 2012, we were able to confirm the decline in placebo patient trial ARRs. They decreased by 25 % per decade. (p < 0.001)



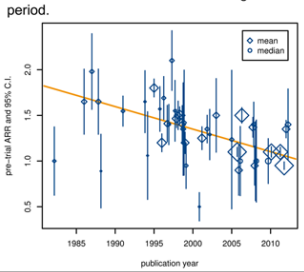
TRENDS OVER TIME

In the next step, we extracted all data on eligibility criteria and patient baseline characteristics looking for evidence for **time trends in the studies' design features**. Setting the significance level at 5%, we discovered the following trends:

- baseline pre-trial ARR decreased by nearly 0.8 over the last 30 years.
(-0.025/year, p < 0.001)
- baseline age increased by one additional year every five years.
(0.198 years/year, p < 0.001)
- baseline MS duration increased by one additional year every 8 years.
(0.122 years/year, p=0.048)
- the number of years, over which the pre-trial ARR was calculated, decreased from 1982 up to today by 1.5 years.
(-0.049 years/year, p < 0.001)
- the number of eligibility criteria increased by three criteria every four years.
(0.769 criteria/year, p < 0.001)

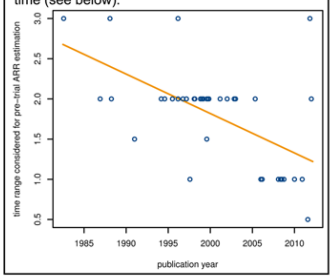
BASELINE PRE-TRIAL ARR

The figure below shows the **decrease of pre-trial ARR by 0.8 over the last 30 years**, using the ARR calculated over the longest time period.



CALCULATING PRE-TRIAL ARR

In order to estimate the ARR at each new study's baseline, patients are asked for the number of relapses in a certain preceding time span, e.g. the previous year or two years. We found this time span to have shortened significantly over time (see below).



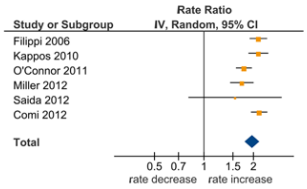
COMPARING PRE-TRIAL ARRS ❶

In a subset of seven studies that offered two baseline pre-trial ARRs, one calculated over the time of the previous one year, another calculated over the previous two years, we compared the results, which showed an apparent **increase in ARR when calculated over shorter time**; in our trials by more than 30%. Assuming this effect to be non-varying, this could cause an overestimation of pre-trial ARRs of up to 43%.
We compared the pre-trial ARRs of the year before the start of the trial with the pre-trial ARR of the year before that, which could be computed from the data provided.

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Random, 95% CI
Filippi 2006	0.7621401	0.05914688	20.3%	2.14 [1.91, 2.41]
Kappos 2010	0.7621401	0.06772265	18.7%	2.14 [1.88, 2.45]
O'Connor 2011	0.5596158	0.05370245	21.3%	1.75 [1.58, 1.94]
Miller 2012	0.5306283	0.0803999	16.5%	1.70 [1.45, 1.99]
Saida 2012	0.4353181	0.33002199	2.3%	1.55 [0.81, 2.95]
Comi 2012	0.7731899	0.05540251	20.9%	2.17 [1.94, 2.42]
Total (95% CI)			100.0%	1.97 [1.78, 2.18]

Heterogeneity: Tau² = 0.01; Chi² = 15.24, df = 5 (P = 0.009); I² = 67%
Test for overall effect: Z = 13.07 (P < 0.00001)

COMPARING PRE-TRIAL ARRS ❷



These pre-trial ARRs, each calculated over one year, differ to a degree that, from a medical perspective, lacks explanation.
We suspect the shortening of the time period considered for the estimation of the pre-trial ARR to cause a regression to the mean effect and with that lead to an **overestimation of ARRs in the patient recruitment process.**

CONCLUSIONS

As the pre-trial ARRs decrease, it is only logical to expect decreasing trial ARRs in placebo patients.
The underlying cause of the decreasing pre-trial ARRs could possibly lie in the increasing duration of illness and, correspondingly, the increasing mean age of the patients, as Tremlet et al. [3] were able to correlate the former with decreasing ARRs in 2008.
In addition, our findings show that the observed decrease in trial ARRs might at least in part be an artefact due to trends in patient recruitment, in particular the decreasing time span over which pre-trial ARRs are calculated at baseline.
To further quantify the impact of our findings on the decreasing trial ARR in placebo patients, we are currently working on a **meta-regression** that may yield more conclusive insights.

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DISCLOSURE

SM Steinvorth has no conflict of interest to disclose. R Nicholas has no conflict of interest to disclose. C Röver has no conflict of interest to disclose. S Schneider has no conflict of interest to disclose. S Straube has no conflict of interest to disclose. T Friede has no conflict of interest to disclose, either.

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10.2 Tabulated summaries of analyzed trials

In the following, *Definition of MS* corresponds to the stated publication providing the criteria for the diagnosis of multiple sclerosis. If in any category no data was available, this was indicated with a dash.

study ID #1

Gonsette et al. 1982

General information

Title	Modulation of immunity in multiple sclerosis: a double-blind levamisole-placebo controlled study in 85 patients		
Authors	Gonsette RE, Demonty L, Delmotte P, Decree J, De Cock W, Verhaeghen H, Symoens J		
Date of publication	1982	*Journal / Reference*	J Neurol 228 (1): 65-72
Score on the OQS	3		
Definition of MS	Schumacher 1965		

Intervention

Treatment arms (Allocation ratio)	Placebo; 150 mg/d Levamisole, then 150 mg/w Levamisole (1:1)		
Trial ARR of the placebo group (SD)	1.23	*Number of patients considered for calculation of trial ARR*	13
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	16+	*Score on the EDSS*	-
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	2	*Words / characters describing the eligibility criteria*	18 / 86
Eligible courses of MS	RRMS + PRMS + progressive MS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	-	*Number of patients (females)*	-
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #2

Mertin et al. 1982

General information

Title	Double-blind controlled trial of immunosuppression in the treatment of multiple sclerosis: final report		
Authors	Mertin J, Rudge P, Kremer M, Healey MJ, Knight SC, Compston A, Batchelor JR, Thompson EJ, Halliday AM, Denman M, Medawar PB		
Date of publication	Aug 1982	*Journal / Reference*	Lancet 2 (8294): 351-4
Score on the OQS	3		
Definition of MS	McAlpine 1972		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3 mg/kg/d Azathioprine (1:1)		
Trial ARR of the placebo group (SD)	1.018	*Number of patients considered for calculation of trial ARR*	22
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	15 months

Eligibility criteria

Age	15 – 45	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	3
Number of eligibility criteria	4	*Words / characters describing the eligibility criteria*	62 / 292
Eligible courses of MS	Relapsing MS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	22	*Number of patients (females)*	43
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1	*Mean pre-trial ARR (SD)*	1
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #3

Camenga et al. 1986

General information

Title	Systemic recombinant alpha-2 interferon therapy in relapsing multiple sclerosis		
Authors	Camenga DL, Johnson KP, Alter M, Engelhardt CD, Fishman PS, Greenstein JI, Haley AS, Hirsch RL, Kleiner JE, Kofie VY, et al.		
Date of publication	Dec 1986	*Journal / Reference*	Arch Neurol 43 (12): 1239-46
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 6 MIU/w IFN-alpha-2 (1:1)		
Trial ARR of the placebo group (SD)	0.8	*Number of patients considered for calculation of trial ARR*	50
Primary outcome	EDSS / Relapse-related / Toxic effects	*Duration of placebo-controlled follow-up*	1 year

Eligibility criteria

Age	20 – 50	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	2 months
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	85 / 488
Eligible courses of MS	RRMS + PRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	50 (32)	*Number of patients (females)*	98 (58)
Mean age (SD) in years	29.4	*Mean age (SD) in years*	28.073
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	3.1	*Mean MS duration (SD) in years*	3.492
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.65	*Mean pre-trial ARR (SD)*	1.699
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.9	*Mean score on the EDSS (SD)*	1.304
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #4

Jacobs et al. 1987

General information

Title	Intrathecally Administered Natural Human Fibroblast Interferon Reduces Exacerbations of Multiple Sclerosis		
Authors	Jacobs L, Salazar AM, Herndon R, Reese PA, Freeman A, Josefowicz R, Cuetter A, Husain F, Smith WA, Ekes R, O'Malley JA		
Date of publication	Jun 1987	*Journal / Reference*	Arch Neurol 44 (6): 589-95
Score on the OQS	5		
Definition of MS	McDonald 1975; Rose, 1970; Poser, 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 9 MIRU IFN-beta intrathecally (1:1)		
Trial ARR of the placebo group (SD)	1.48	*Number of patients considered for calculation of trial ARR*	35
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	-	*Score on the EDSS*	-
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	1	*Words / characters describing the eligibility criteria*	21 / 126
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	35 (25)	*Number of patients (females)*	69 (48)
Mean age (SD) in years	33 (7.2)	*Mean age (SD) in years*	32.162 (6.821)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.1	*Mean MS duration (SD) in years*	5.755 (3.739)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	4.3 (2.3)	*Mean score on the EDSS (SD)*	4.251 (2.284)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #5

Hirsch et al. 1988

General information

Title	The placebo effect during a double blind trial of recombinant alpha 2 interferon in multiple sclerosis patients: immunological and clinical findings		
Authors	Hirsch RL, Johnson KP, Camenga DL		
Date of publication	Apr 1988	*Journal / Reference*	Int J Neurosci 39 (3-4): 189-96
Score on the OQS	3		
Definition of MS	-		

Intervention

Treatment arms (Allocation ratio)	Placebo; IFNalpha-2 (1:1)		
Trial ARR of the placebo group (SD)	0.775	*Number of patients considered for calculation of trial ARR*	50
Primary outcome	Natural killer cell activity	*Duration of placebo-controlled follow-up*	52 weeks

Eligibility criteria

Age	-	*Score on the EDSS*	-
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	2	*Words / characters describing the eligibility criteria*	28 / 156
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	50	*Number of patients (females)*	98
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.65	*Mean pre-trial ARR (SD)*	1.7
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #6

Milanese et al. 1988

General information

Title	Double blind controlled randomized study on azathioprine efficacy in multiple sclerosis. Preliminary results		
Authors	Milanese C, La Mantia L, Salmaggi A, Campi A, Bortolami C, Tajoli L, Nespolo A, Corridori F		
Date of publication	Feb 1988	*Journal / Reference*	Ital J Neurol Sci 9 (1): 53-7
Score on the OQS	5		
Definition of MS	Schumacher 1965		

Intervention

Treatment arms (Allocation ratio)	Placebo; 2 – 2.5 mg/kg/d Azathioprine (1:1)		
Trial ARR of the placebo group (SD)	0.92	*Number of patients considered for calculation of trial ARR*	7
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	3 years

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 7
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	0.667	*Time considered for calculation of pre-trial ARR in years*	3
Number of eligibility criteria	7	*Words / characters describing the eligibility criteria*	120 / 713
Eligible courses of MS	RRMS + progressive MS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	7	*Number of patients (females)*	13
Mean age (SD) in years	34.1	*Mean age (SD) in years*	33.639
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	7	*Mean MS duration (SD) in years*	7
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.43	*Mean score on the EDSS (SD)*	2.31
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #7

Goodkin et al. 1991

General information

Title	The efficacy of azathioprine in relapsing-remitting multiple sclerosis		
Authors	Goodkin DE, Bailly RC, Teetzen ML, Hertsgaard D, Beatty WW		
Date of publication	Jan 1991	*Journal / Reference*	Neurology 41 (1): 20-5
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3 mg/kg Azathioprine (1:1)		
Trial ARR of the placebo group (SD)	0.94 (0.847)	*Number of patients considered for calculation of trial ARR*	25
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	2 – 6.5
Relapse-free time before baseline	1 month	*Steroid-free time before baseline*	1 month
Minimum pre-trial ARR	1.333	*Time considered for calculation of pre-trial ARR in years*	1.5
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	169 / 925
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	25 (17)	*Number of patients (females)*	54 (36)
Mean age (SD) in years	36.28	*Mean age (SD) in years*	35.979
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.24 (8.34)	*Mean MS duration (SD) in years*	6.278 (7.076)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.547 (0.42)	*Mean pre-trial ARR (SD)*	1.554 (0.389)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.72 (1.6)	*Mean score on the EDSS (SD)*	3.43 (1.408)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #8

Bastianello et al. 1994

General information

Title	A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year		
Authors	Bastianello S, Pozzilli C, D'Andrea F, Millefiorini E, Trojano M, Morino S, Gasperini C, Bozzao A, Gallucci M, Andreula C, et al.		
Date of publication	Aug 1994	*Journal / Reference*	Can J Neurol Scl 21 (3): 266-70
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 8 mg/m²/month Mitoxantrone (1:1)		
Trial ARR of the placebo group (SD)	1.67 (1.2)	*Number of patients considered for calculation of trial ARR*	12
Primary outcome	Relapse-related / EDSS	*Duration of placebo-controlled follow-up*	1 year

Eligibility criteria

Age	18 – 45	*Score on the EDSS*	2 – 5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	3 months
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	22	*Words / characters describing the eligibility criteria*	140 / 842
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	12 (7)	*Number of patients (females)*	25 (15)
Mean age (SD) in years	28.5 (6.5)	*Mean age (SD) in years*	29.228 (5.779)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	5 (2.7)	*Mean MS duration (SD) in years*	5.104 (2.496)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.65 (0.6)	*Mean pre-trial ARR (SD)*	1.52 (0.601)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.5 (1)	*Mean score on the EDSS (SD)*	3.604 (0.845)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #9

Durelli et al. 1994

General information

Title	Chronic systemic high-dose recombinant interferon alfa-2a reduces exacerbation rate, MRI signs of disease activity, and lymphocyte interferon gamma production in relapsing-remitting multiple sclerosis		
Authors	Durelli L, Bongioanni MR, Cavallo R, Ferrero B, Ferri R, Ferrio MF, Bradac GB, Riva A, Vai S, Geuna M, et al.		
Date of publication	Mar 1994	*Journal / Reference*	Neurology 44 (3 Pt 1): 406-13
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 9 MIU/2d rIFNalpha-2a i.m. (2:3)		
Trial ARR of the placebo group (SD)	2 (1.527)	*Number of patients considered for calculation of trial ARR*	8
Primary outcome	Relapse-related / MRI-related / EDSS / hematological	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	3 months	*Steroid-free time before baseline*	3 months
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	91 / 504
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	8 (4)	*Number of patients (females)*	20 (11)
Mean age (SD) in years	38 (11.709)	*Mean age (SD) in years*	35 (9.078)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.37 (2.771)	*Mean MS duration (SD) in years*	7.9 (4.306)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.06 (0.693)	*Mean pre-trial ARR (SD)*	1.174 (0.952)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.81 (1.628)	*Mean score on the EDSS (SD)*	3.176 (0.952)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #10

The IFNB Multiple Sclerosis Study Group et al. 1995

General information

Title	Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial
Authors	The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group

Date of publication	Jul 1995	Journal / Reference	Neurology 45 (7): 1277-85
Score on the OQS	4		Neurology 43: 655-667
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 1.6 MIU IFNbeta-1b; 8 MIU IFNbeta-1b (1:1:1)		
Trial ARR of the placebo group (SD)	1.12 (1.329)	*Number of patients considered for calculation of trial ARR*	123
Primary outcome	Relapse-related, EDSS	*Duration of placebo-controlled follow-up*	5 years

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	106 / 546
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	123 (88)	*Number of patients (females)*	372 (259)
Mean age (SD) in years	36 (6.654)	*Mean age (SD) in years*	35.498 (7.087)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	3.9 (3.327)	*Mean MS duration (SD) in years*	4.436 (4.14)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.8 (0.555)	*Mean pre-trial ARR (SD)*	1.716 (0.795)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.8 (1.109)	*Mean score on the EDSS (SD)*	2.9 (2.771)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #11

Andersen et al. 1996

General information

Title	Linomide reduces the rate of active lesions in relapsing-remitting multiple sclerosis		
Authors	Andersen O, Lycke J, Tollesson PO, Svenningsson A, Runmarker B, Linde AS, Aström M, Gjörstrup P, Ekholm S		
Date of publication	Oct 1996	*Journal / Reference*	Neurology 47 (4): 895-900
Score on the OQS	4		
Definition of MS	Poser 1984		

Intervention

Treatment arms (Allocation ratio)	Placebo; 2.5 mg/d Linomide (1:1)		
Trial ARR of the placebo group (SD)	1.087	*Number of patients considered for calculation of trial ARR*	14
Primary outcome	Adverse events	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	1 – 4
Relapse-free time before baseline	1 month	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	5	*Words / characters describing the eligibility criteria*	54 / 269
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	14 (11)	*Number of patients (females)*	28 (20)
Mean age (SD) in years	32	*Mean age (SD) in years*	31.5
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	2.14 (2.17)	*Mean MS duration (SD) in years*	3.57 (3.841)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.57 (0.468)	*Mean pre-trial ARR (SD)*	1.588 (0.58)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.21 (0.973)	*Mean score on the EDSS (SD)*	2.265 (0.92)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #12

Jacobs et al. 1996

General information

Title	Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis		
Authors	Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE 3rd, Priore RL, Pullicino PM, Scherokman BJ, Whitham RH, et al.		
Date of publication	Mar 1996	*Journal / Reference*	Ann Neurol 39 (3): 285-94
Score on the OQS	4		
Definition of MS	Poser 1983; Hauser 1994		

Intervention

Treatment arms (Allocation ratio)	Placebo; 30 µg/w IFNbeta-1a (1:1)		
Trial ARR of the placebo group (SD)	0.82	*Number of patients considered for calculation of trial ARR*	143
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	156 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	1 – 3.5
Relapse-free time before baseline	2 months	*Steroid-free time before baseline*	2 months
Minimum pre-trial ARR	0.667	*Time considered for calculation of pre-trial ARR in years*	3
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	107 / 643
Eligible courses of MS	Relapsing		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	143 (103)	*Number of patients (females)*	301 (221)
Mean age (SD) in years	36.9 (7.653)	*Mean age (SD) in years*	36.795 (7.389)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.4 (5.86)	*Mean MS duration (SD) in years*	6.505 (5.81)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.3 (0.837)	*Mean score on the EDSS (SD)*	2.353 (0.795)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #13

Lycke et al. 1996

General information

Title	Acyclovir treatment of relapsing-remitting multiple sclerosis. A randomized, placebo-controlled, double-blind study		
Authors	Lycke J, Svennerholm B, Hjelmquist E, Frisén L, Badr G, Andersson M, Vahlne A, Andersen O		
Date of publication	Mar 1996	*Journal / Reference*	J Neurol 243 (3): 214-24
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3x 800 mg/d Acyclovir (1:1)		
Trial ARR of the placebo group (SD)	1.57	*Number of patients considered for calculation of trial ARR*	30
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 45	*Score on the EDSS*	0 – 3.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	12	*Words / characters describing the eligibility criteria*	135 / 821
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	30 (23)	*Number of patients (females)*	60 (40)
Mean age (SD) in years	33.13 (6.956)	*Mean age (SD) in years*	32.78 (7.21)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.17 (6.573)	*Mean MS duration (SD) in years*	5.8 (6.42)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.69 (0.657)	*Mean pre-trial ARR (SD)*	1.72 (0.769)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	1.88 (0.603)	*Mean score on the EDSS (SD)*	1.84 (0.715)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #14

Fazekas et al. 1997

General information

Title	Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis		
Authors	Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B		
Date of publication	Mar 1997	*Journal / Reference*	Lancet 349 (9052): 589-93
Score on the OQS	5		
Definition of MS	Poser 1983; Hauser 1994		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.15 – 0.2 mg/kg/month IVIg (1:1)		
Trial ARR of the placebo group (SD)	1.26 (2.223)	*Number of patients considered for calculation of trial ARR*	73
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	15 – 64	*Score on the EDSS*	1 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	2 weeks
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	142 / 803
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	73 (54)	*Number of patients (females)*	148 (111)
Mean age (SD) in years	37.3 (10.026)	*Mean age (SD) in years*	36.996 (10.292)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	7.3 (5.667)	*Mean MS duration (SD) in years*	7.047 (5.262)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.37 (1.744)	*Mean score on the EDSS (SD)*	3.3 (1.541)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #15

Millefiorini et al. 1997

General information

Title	Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome		
Authors	Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, Morino S, Morra VB, Bozzao A, Calo A, Bernini ML, Gambi D, Prencipe M		
Date of publication	Mar 1997	*Journal / Reference*	J Neurol 244 (3): 153-9
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 12x 8 mg/m²/month Mitoxantrone (1:1)		
Trial ARR of the placebo group (SD)	1.31 (0.95)	*Number of patients considered for calculation of trial ARR*	24
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 45	*Score on the EDSS*	2 – 5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	3 months
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	20	*Words / characters describing the eligibility criteria*	128 / 779
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	24 (18)	*Number of patients (females)*	51 (35)
Mean age (SD) in years	28.7 (6.5)	*Mean age (SD) in years*	29.865 (6.276)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	5 (3)	*Mean MS duration (SD) in years*	5.371 (2.991)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.4 (0.55)	*Mean pre-trial ARR (SD)*	1.4 (0.571)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.5 (1.2)	*Mean score on the EDSS (SD)*	3.553 (0.768)
Median score on the (IQR)	3.5	*Median score on the (IQR)*	-

study ID #16

Miller et al. 1997

General information

Title	A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis		
Authors	Miller AE, Morgante LA, Buchwald LY, Nutile SM, Coyle PK, Krupp LB, Doscher CA, Lublin FD, Knobler RL, Trantas F, Kelley L, Smith CR, La Rocca N, Lopez S		
Date of publication	Feb 1997	*Journal / Reference*	Neurology 48 (2): 312-4
Score on the OQS	3		
Definition of MS	-		

Intervention

Treatment arms (Allocation ratio)	Placebo; 1x Influenza-vaccination (1:2)		
Trial ARR of the placebo group (SD)	0.22	*Number of patients considered for calculation of trial ARR*	54
Primary outcome	Occurrence of Influenza	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	9	*Words / characters describing the eligibility criteria*	92 / 516
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	54	*Number of patients (females)*	103
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #17

Van Oosten et al. 1997

General information

Title	Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial		
Authors	Van Oosten BW, Lai M, Hodgkinson S, Barkhof F, Miller DH, Moseley IF, Thompson AJ, Rudge P, McDougall A, McLeod JG, Adèr HJ, Polman CH		
Date of publication	Aug 1997	*Journal / Reference*	Neurology 49 (2): 351-7 Multiple Sclerosis 1 (6): 339-342
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 6x 50 mg/month cM-T412 (1:1)		
Trial ARR of the placebo group (SD)	1.8 (1.393)	*Number of patients considered for calculation of trial ARR*	36
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	18 months

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	3 – 7
Relapse-free time before baseline	2 months	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	2	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	25	*Words / characters describing the eligibility criteria*	253 / 1466
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	36 (23)	*Number of patients (females)*	71 (39)
Mean age (SD) in years	36.8 (6.7)	*Mean age (SD) in years*	36.849 (6.901)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.4 (6.2)	*Mean MS duration (SD) in years*	6.548 (5.872)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	2.1 (1)	*Mean pre-trial ARR (SD)*	1.804 (1.038)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	5	*Median score on the (IQR)*	-

study ID #18

Achiron et al. 1998

General information

Title	Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses		
Authors	Achiron A, Gabbay U, Gilad R, Hassin-Baer S, Barak Y, Gornish M, Elizur A, Goldhammer Y, Sarova-Pinhas I		
Date of publication	Feb 1998	*Journal / Reference*	Neurology 50 (2): 398-402
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.4 g/kg/d IVIg every other month (1:1)		
Trial ARR of the placebo group (SD)	1.61 (0.857)	*Number of patients considered for calculation of trial ARR*	20
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	0.5	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	68 / 386
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	20 (16)	*Number of patients (females)*	40 (32)
Mean age (SD) in years	33.8 (10.733)	*Mean age (SD) in years*	34.6 (9.987)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	3.95 (2.862)	*Mean MS duration (SD) in years*	4.025 (2.761)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.55 (0.76)	*Mean pre-trial ARR (SD)*	1.7 (0.982)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.82 (1.655)	*Mean score on the EDSS (SD)*	2.86 (1.771)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #19

Johnson et al. 1998

General information

Title	Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability		
Authors	Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB, Vollmer T, Weiner LP, Wolinsky JS		
Date of publication	Mar 1998	*Journal / Reference*	Neurology 50 (3): 701-8
Score on the OQS	4		Neurology 45 (7): 1268-76
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 20 mg/d Glatiramer Acetate (1:1)		
Trial ARR of the placebo group (SD)	0.81	*Number of patients considered for calculation of trial ARR*	126
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	35 months

Eligibility criteria

Age	18 – 45	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	21	*Words / characters describing the eligibility criteria*	157 / 883
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	126 (96)	*Number of patients (females)*	251 (184)
Mean age (SD) in years	34.33 (6.49)	*Mean age (SD) in years*	34.455 (6.225)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.64 (5.09)	*Mean MS duration (SD) in years*	6.944 (4.971)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.465 (0.565)	*Mean pre-trial ARR (SD)*	1.46 (0.597)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.42 (1.28)	*Mean score on the EDSS (SD)*	2.619 (1.25)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #20

Noseworthy et al. 1998

General information

Title	The Mayo Clinic-Canadian Cooperative trial of sulfasalazine in active multiple sclerosis		
Authors	Noseworthy JH, O'Brien P, Erickson BJ, Lee D, Sneve D, Ebers GC, Rice GP, Auty A, Hader WJ, Kirk A, Duquette P, Carter J, Francis G, Metz L, Shuster E		
Date of publication	Nov 1998	*Journal / Reference*	Neurology 51 (5): 1342-52
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 1 week 500 mg/d Sulfasalazine, an additional 500 mg/d per week up to 2 g/d Sulfasalazine (1:1)		
Trial ARR of the placebo group (SD)	1.1	*Number of patients considered for calculation of trial ARR*	79
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	3 years

Eligibility criteria

Age	18+	*Score on the EDSS*	1 – 4
Relapse-free time before baseline	-	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	149 / 889
Eligible courses of MS	RRMS + SPMS + PPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	79 (48)	*Number of patients (females)*	151 (105)
Mean age (SD) in years	26.5	*Mean age (SD) in years*	27.692
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	4	*Mean MS duration (SD) in years*	4.954
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.5	*Mean pre-trial ARR (SD)*	1.5
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2	*Mean score on the EDSS (SD)*	2
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #21

PRISMS Study Group 1998

General information

Title	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis		
Authors	PRISMS Study Group		
Date of publication	Nov 1998	*Journal / Reference*	Lancet 352 (9139): 1498-504
Score on the OQS	5		
Definition of MS	-		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3x 22 µg/w IFNbeta-1a; 3x 44 µg/w IFNbeta-1a (1:1:1)		
Trial ARR of the placebo group (SD)	1.28	*Number of patients considered for calculation of trial ARR*	187
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	9	*Words / characters describing the eligibility criteria*	77 / 448
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	187 (140)	*Number of patients (females)*	560 (386)
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	34.6 (28.8; 40.4)	*Median age (IQR) in years*	34.9 (29.1; 40.4)
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	4.3 (2.4; 8.4)	*Median MS duration (IQR) in years*	5.3 (2.8; 10)
Mean pre-trial ARR (SD)	1.5 (0.65)	*Mean pre-trial ARR (SD)*	1.5 (0.6)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.4 (1.2)	*Mean score on the EDSS (SD)*	2.5 (1.2)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #22

Deisenhammer et al. 1999

General information

Title	Intravenous Immunoglobulins in Multiple Sclerosis: Results of the Austrian Immunoglobulin in Multiple Sclerosis (AIMS) Trial		
Authors	Deisenhammer F, Fazekas F, Strasser-Fuchs S, Nahler G, Mamoli B, AIMS Study Group		
Date of publication	Nov 1999	*Journal / Reference*	Infusionsther Transfusionsmed 26 (Suppl.2): 42-47
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.15 – 0,2 g/kg/month IVIg (1:1)		
Trial ARR of the placebo group (SD)	1.26 (2.2)	*Number of patients considered for calculation of trial ARR*	73
Primary outcome	EDSS	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	15 – 65	*Score on the EDSS*	1 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	2 weeks
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	147 / 734
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	73 (54)	*Number of patients (females)*	148 (111)
Mean age (SD) in years	37.7 (9.8)	*Mean age (SD) in years*	36.996 (10.079)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	7.3 (5.7)	*Mean MS duration (SD) in years*	7.047 (5.16)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.4 (0.9)	*Mean pre-trial ARR (SD)*	1.349 (0.898)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.3 (1.7)	*Mean score on the EDSS (SD)*	3.3 (1.55)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #23

Lenercept Multiple Sclerosis Study Group et al. 1999

General information

Title	TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study		
Authors	The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group		
Date of publication	Aug 1999	*Journal / Reference*	Neurology 53 (3): 457-65
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 10 mg/4w Lenercept; 50 mg/4w Lenercept; 100 mg/4w Lenercept (1:1:1:1)		
Trial ARR of the placebo group (SD)	0.98	*Number of patients considered for calculation of trial ARR*	43
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	11	*Words / characters describing the eligibility criteria*	154 / 843
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	44 (29)	*Number of patients (females)*	168 (124)
Mean age (SD) in years	36.5	*Mean age (SD) in years*	35.288
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.35	*Mean pre-trial ARR (SD)*	1.411
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.45	*Mean score on the EDSS (SD)*	2.583
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #24

Myhr et al. 1999

General information

Title	Interferon-alpha2a reduces MRI disease activity in relapsing-remitting multiple sclerosis		
Authors	Myhr KM, Riise T, Green Lilleås FE, Beiske TG, Celius EG, Edland A, Jensen D, Larsen JP, Nilsen R, Nortvedt MW, Smievoll AI, Vedeler C, Nyland HI		
Date of publication	Mar 1999	*Journal / Reference*	Neurology 52 (5): 1049-56
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3x 4.5 MIU/w IFNalpha-2a; 3x 9 MIU/w IFNalpha-2a (1:1:1)		
Trial ARR of the placebo group (SD)	0.88	*Number of patients considered for calculation of trial ARR*	32
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	1 month
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	102 / 593
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	33 (23)	*Number of patients (females)*	97 (69)
Mean age (SD) in years	36.7	*Mean age (SD) in years*	34.69
Median age (IQR) in years	36	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	5.5	*Mean MS duration (SD) in years*	6.853
Median MS duration (IQR) in years	5	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.42	*Mean pre-trial ARR (SD)*	1.338
Median pre-trial ARR (IQR)	1.5	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.73	*Mean score on the EDSS (SD)*	2.842
Median score on the (IQR)	2.5	*Median score on the (IQR)*	-

study ID #25

OWIMS Study Group 1999

General information

Title	Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study		
Authors	The Once Weekly Interferon for MS Study Group		
Date of publication	Sep 1999	*Journal / Reference*	Neurology 53 (4): 679-86
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 22 µg/w IFNbeta-1a; 44 µg/w IFNbeta-1a (1:1:1)		
Trial ARR of the placebo group (SD)	1.174 (1.25)	*Number of patients considered for calculation of trial ARR*	100
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	48 weeks

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	8 weeks	*Steroid-free time before baseline*	8 weeks
Minimum pre-trial ARR	0.5	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	17	*Words / characters describing the eligibility criteria*	122 / 629
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	100 (74)	*Number of patients (females)*	293 (213)
Mean age (SD) in years	34.9 (7.8)	*Mean age (SD) in years*	35.263 (7.486)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.3 (4.7)	*Mean MS duration (SD) in years*	6.628 (5.026)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.2 (0.6)	*Mean pre-trial ARR (SD)*	1.2 (0.599)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.6 (1.3)	*Mean score on the EDSS (SD)*	2.632 (1.3)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #26

Patti et al. 1999

General information

Title	Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study		
Authors	Patti F, L'Episcopo MR, Cataldi ML, Reggio A		
Date of publication	Nov 1999	*Journal / Reference*	Acta Neurol Scand 100 (5): 283-9
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3x 6 MIU/w IFNbeta (1:1)		
Trial ARR of the placebo group (SD)	0.31	*Number of patients considered for calculation of trial ARR*	29
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 45	*Score on the EDSS*	0 – 3.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	17	*Words / characters describing the eligibility criteria*	166 / 863
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	29 (17)	*Number of patients (females)*	58 (34)
Mean age (SD) in years	36.6	*Mean age (SD) in years*	36.6
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	9.7	*Mean MS duration (SD) in years*	9.8
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	0.95	*Mean pre-trial ARR (SD)*	0.925
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.1	*Mean score on the EDSS (SD)*	3.08
-Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #27

Romine et al. 1999

General information

Title	A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis		
Authors	Romine JS, Sipe JC, Koziol JA, Zyroff J, Beutler E		
Date of publication	Jan 1999	*Journal / Reference*	Proc Assoc Am Physicians 111 (1): 35-44
Score on the OQS	5		
Definition of MS	-		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.07 mg/kg/d Cladribine (1:1)		
Trial ARR of the placebo group (SD)	1.34 (1.145)	*Number of patients considered for calculation of trial ARR*	25
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	18 months

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	13	*Words / characters describing the eligibility criteria*	101 / 605
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	25 (18)	*Number of patients (females)*	52 (36)
Mean age (SD) in years	39.8	*Mean age (SD) in years*	41.669
Median age (IQR) in years	41 (36.5; 44)	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	9.1	*Mean MS duration (SD) in years*	9.671
Median MS duration (IQR) in years	9 (3.5; 12.5)	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.8	*Mean score on the EDSS (SD)*	3.852
Median score on the (IQR)	3.5 (2.5; 5.3)	*Median score on the (IQR)*	-

study ID #28

Tubridy et al. 1999

General information

Title	The effect of anti-alpha4 integrin antibody on brain lesion activity in MS		
Authors	Tubridy N, Behan PO, Capildeo R, Chaudhuri A, Forbes R, Hawkins CP, Hughes RA, Palace J, Sharrack B, Swingler R, Young C, Moseley IF, MacManus DG, Donoghue S, Miller DH		
Date of publication	Aug 1999	*Journal / Reference*	Neurology 53 (3): 466-72
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3 mg/kg Natalizumab (1:1)		
Trial ARR of the placebo group (SD)	1.052	*Number of patients considered for calculation of trial ARR*	31
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	2 – 7
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	1.333	*Time considered for calculation of pre-trial ARR in years*	1.5
Number of eligibility criteria	21	*Words / characters describing the eligibility criteria*	132 / 803
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	35 (21)	*Number of patients (females)*	72 (46)
Mean age (SD) in years	40.8	*Mean age (SD) in years*	40.338
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	9.933	*Mean MS duration (SD) in years*	9.848
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	4.7	*Mean score on the EDSS (SD)*	4.803
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #29

Brod et al. 2001

General information

Title	Ingested IFN-alpha: results of a pilot study in relapsing-remitting MS		
Authors	Brod SA, Lindsey JW, Vriesendorp FS, Ahn C, Henninger E, Narayana PA, Wolinsky JS		
Date of publication	Sep 2001	*Journal / Reference*	Neurology 57 (5): 845-52
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 10 kIU/2d IFNalpha-2a, 30 kIU/2d IFNalpha-2a (1:1:1)		
Trial ARR of the placebo group (SD)	0.267	*Number of patients considered for calculation of trial ARR*	10
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	9 months

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	1 month
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	80 / 439
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	10 (8)	*Number of patients (females)*	29 (24)
Mean age (SD) in years	43 (5.4)	*Mean age (SD) in years*	42.559 (7.185)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	0.5 (0.25)	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.2 (1.7)	*Mean score on the EDSS (SD)*	2.662 (1.424)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #30

Comi et al. 2001

General information

Title	European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis		
Authors	Comi G, Filippi M, Wolinsky JS		
Date of publication	Mar 2001	*Journal / Reference*	Ann Neurol 49 (3): 290-7
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 20 mg/d Glatiramer Acetate (1:1)		
Trial ARR of the placebo group (SD)	1.21	*Number of patients considered for calculation of trial ARR*	120
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	9 months

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	0.5	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	26	*Words / characters describing the eligibility criteria*	184 / 975
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	120	*Number of patients (females)*	239
Mean age (SD) in years	34 (7.5)	*Mean age (SD) in years*	34.05 (7.435)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.3 (5.5)	*Mean MS duration (SD) in years*	8.101 (5.492)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.25 (0.7)	*Mean pre-trial ARR (SD)*	1.325 (0.808)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.4 (1.2)	*Mean score on the EDSS (SD)*	2.35 (1.15)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #31

Bech et al. 2002

General information

Title	A randomized, double-blind, placebo-controlled MRI study of anti-herpes virus therapy in MS		
Authors	Bech E, Lycke J, Gadeberg P, Hansen HJ, Malmeström C, Andersen O, Christensen T, Ekholm S, Haahr S, Höllsberg P et al.		
Date of publication	Jan 2002	*Journal / Reference*	Neurology 58 (1): 31-6
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3 g/d Valacyclovir (1:1)		
Trial ARR of the placebo group (SD)	1.407	*Number of patients considered for calculation of trial ARR*	34
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	25	*Words / characters describing the eligibility criteria*	207 / 1156
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	34 (21)	*Number of patients (females)*	70 (44)
Mean age (SD) in years	33.1 (7.2)	*Mean age (SD) in years*	34.6 (8.7)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	9.5 (5.8)	*Mean MS duration (SD) in years*	9.5 (6)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.35 (0.45)	*Mean pre-trial ARR (SD)*	1.3 (0.45)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	3	*Median score on the (IQR)*	2.5

study ID #32

Lewańska et al. 2002

General information

Title	No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment		
Authors	Lewańska M, Siger-Zajdel M, Selmaj K		
Date of publication	Nov 2002	*Journal / Reference*	Eur J Neurol 9 (6): 565-72
Score on the OQS	4		
Definition of MS	Poser 1983; Paty 1988		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.2 g/kg/d IVIg; 0.4 g/kg/d IVIg (1:1:1)		
Trial ARR of the placebo group (SD)	1.24 (0.75)	*Number of patients considered for calculation of trial ARR*	18
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	1 year

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	3 months	*Steroid-free time before baseline*	3 months
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	20	*Words / characters describing the eligibility criteria*	147 / 801
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	17 (7)	*Number of patients (females)*	49 (29)
Mean age (SD) in years	41.8 (6.98)	*Mean age (SD) in years*	37.206 (7.907)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	7.5 (4.7)	*Mean MS duration (SD) in years*	8.518 (6.15)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.97 (1.58)	*Mean score on the EDSS (SD)*	2.99 (2.193)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #33

Miller et al. 2003

General information

Title	A controlled trial of natalizumab for relapsing multiple sclerosis		
Authors	Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Connor PW; International Natalizumab Multiple Sclerosis Trial Group		
Date of publication	Jan 2003	*Journal / Reference*	N Engl J Med 348 (1): 15-23
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3 mg/kg Natalizumab; 6 mg/kg Natalizumab (1:1:1)		
Trial ARR of the placebo group (SD)	0.507	*Number of patients considered for calculation of trial ARR*	71
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	2 – 6.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	-	*Words / characters describing the eligibility criteria*	117 / 636
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	71 (46)	*Number of patients (females)*	213 (152)
Mean age (SD) in years	42.9	*Mean age (SD) in years*	43.563
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	10.2	*Mean MS duration (SD) in years*	11.655
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.5	*Mean pre-trial ARR (SD)*	1.501
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	4.4	*Mean score on the EDSS (SD)*	4.301
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #34

Wroe 2005

General information

Title	Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis.		
Authors	Wroe SJ		
Date of publication	May 2005	*Journal / Reference*	J Int Med Res 33 (3): 309-18
Score on the OQS	4		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; IFNbeta-1b 8 MIU (1:2)		
Trial ARR of the placebo group (SD)	1.091	*Number of patients considered for calculation of trial ARR*	33
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	3 months

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	1 month
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	32	*Words / characters describing the eligibility criteria*	228 / 1308
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	33 (24)	*Number of patients (females)*	98 (72)
Mean age (SD) in years	38	*Mean age (SD) in years*	36.01
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.235	*Mean pre-trial ARR (SD)*	1.298
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.09	*Mean score on the EDSS (SD)*	2.977
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #35

Filippi et al. 2006

General information

Title	Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study		
Authors	Filippi M, Wolinsky JS, Comi G; CORAL Study Group		
Date of publication	Jan 2006	*Journal / Reference*	Lancet Neurol 5 (3): 213-20
Score on the OQS	5		
Definition of MS	Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 5 mg/d Glatiramer Acetate; 50 mg/d Glatiramer Acetate (1:1:1)		
Trial ARR of the placebo group (SD)	0.568	*Number of patients considered for calculation of trial ARR*	548
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	56 weeks

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	28	*Words / characters describing the eligibility criteria*	212 / 1209
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	548 (401)	*Number of patients (females)*	1644 (1219)
Mean age (SD) in years	36.6 (7.7)	*Mean age (SD) in years*	36.498 (7.675)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	7.7 (6.2)	*Mean MS duration (SD) in years*	7.662 (6.167)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.5 (0.8) 2 year period: 1.1 (0.6)	*Mean pre-trial ARR (SD)*	1 year period: 1.5 (0.734) 2 year period: 1.084 (0.584)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.3 (1.2)	*Mean score on the EDSS (SD)*	2.266 (1.135)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #36

Kappos et al. 2006

General information

Title	Oral fingolimod (FTY720) for relapsing multiple sclerosis.		
Authors	Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, Haas T, Korn AA, Karlsson G, Radue EW		
Date of publication	Sep 2006	*Journal / Reference*	N Engl J Med 355 (11): 1124-40
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 1.25 mg/d Fingolimod; 5 mg/d Fingolimod (1:1:1)		
Trial ARR of the placebo group (SD)	0.77	*Number of patients considered for calculation of trial ARR*	92
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	Complex
Number of eligibility criteria	15	*Words / characters describing the eligibility criteria*	191 / 1035
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	92 (61)	*Number of patients (females)*	277 (196)
Mean age (SD) in years	37.1	*Mean age (SD) in years*	37.801
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.4	*Mean MS duration (SD) in years*	8.833
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.2 2 year period: 0.9	*Mean pre-trial ARR (SD)*	1 year period: 1.267 2 year period: 0.933
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.6	*Mean score on the EDSS (SD)*	2.6
Median score on the (IQR)	2	*Median score on the (IQR)*	-

study ID #37

O'Connor et al. 2006

General information

Title	A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses		
Authors	O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, Paty DW, Stewart JA, Scheyer R; Teriflunomide Multiple Sclerosis Trial Group; University of British Columbia MS/MRI Research Group		
Date of publication	Mar 2006	*Journal / Reference*	Neurology 66 (6): 894-900
Score on the OQS	4		
Definition of MS	Poser 1983; Paty 1988		

Intervention

Treatment arms (Allocation ratio)	Placebo; 7 mg/d Teriflunomide; 14 mg/d Teriflunomide (1:1:1)		
Trial ARR of the placebo group (SD)	0.81 (1.22)	*Number of patients considered for calculation of trial ARR*	61
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	252

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	Complex	*Time considered for calculation of pre-trial ARR in years*	Complex
Number of eligibility criteria	10	*Words / characters describing the eligibility criteria*	95 / 528
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	61 (41)	*Number of patients (females)*	179 (132)
Mean age (SD) in years	39.2 (8.7)	*Mean age (SD) in years*	39.793 (8.995)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.6 (7.9)	*Mean MS duration (SD) in years*	9.148 (7.727)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	2.5	*Median score on the (IQR)*	-

study ID #38

Polman et al. 2006

General information

Title	A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis		
Authors	Polman CH, O'Connor PW, Havrdová E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators		
Date of publication	Mar 2006	*Journal / Reference*	N Engl J Med 354 (9): 899-910
Score on the OQS	5		
Definition of MS	McDonald 2001; Lublin 1996		

Intervention

Treatment arms (Allocation ratio)	Placebo; 300 mg/4w Natalizumab (1:2)		
Trial ARR of the placebo group (SD)	0.64	*Number of patients considered for calculation of trial ARR*	315
Primary outcome	Relapse-related / EDSS	*Duration of placebo-controlled follow-up*	120 weeks

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	50 days	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	15	*Words / characters describing the eligibility criteria*	172 / 969
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	315 (211)	*Number of patients (females)*	942 (660)
Mean age (SD) in years	36.7 (7.8)	*Mean age (SD) in years*	36 (8.3)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	6	*Median MS duration (IQR) in years*	5
Mean pre-trial ARR (SD)	1.5 (0.77)	*Mean pre-trial ARR (SD)*	1.52 (0.86)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.3 (1.2)	*Mean score on the EDSS (SD)*	2.3 (1.2)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #39

Broadley et al. 2008

General information

Title	Results of a phase IIa clinical trial of an anti-inflammatory molecule, chaperonin 10, in multiple sclerosis.		
Authors	Broadley SA, Vanags D, Williams B, Johnson B, Feeney D, Griffiths L, Shakib S, Brown G, Coulthard A, Mullins P, Kneebone C		
Date of publication	Nov 2008	*Journal / Reference*	Mult Scler 15 (3): 329-36
Score on the OQS	5		
Definition of MS	McDonald 2001; Paty 1988		

Intervention

Treatment arms (Allocation ratio)	Placebo; 5 mg/w Chaperonin10; 10 mg/w Chaperonin10 (1:2:2)		
Trial ARR of the placebo group (SD)	0.395	*Number of patients considered for calculation of trial ARR*	11
Primary outcome	Adverse events	*Duration of placebo-controlled follow-up*	12 weeks

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	22	*Words / characters describing the eligibility criteria*	213 / 1201
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	11 (7)	*Number of patients (females)*	50 (37)
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	49	*Median age (IQR) in years*	46
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	3.5	*Median score on the (IQR)*	3.5

study ID #40

Comi et al. 2008

General information

Title	Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study		
Authors	Comi G, Pulizzi A, Rovaris M, Abramsky O, Arbizu T, Boiko A, Gold R, Havrdová E, Komoly S, Selmaj K, Sharrack B, Filippi M; LAQ/5062 Study Group		
Date of publication	Jun 2008	*Journal / Reference*	Lancet 371 (9630): 2085-92
Score on the OQS	5		
Definition of MS	Polman 2005; Lublin 1996		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.3 mg Laquinimod; 0.6 mg Laquinimod (1:1:1)		
Trial ARR of the placebo group (SD)	0.77 (1.25)	*Number of patients considered for calculation of trial ARR*	102
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	36 weeks

Eligibility criteria

Age	18 – 50	*Score on the EDSS*	1 – 5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	31	*Words / characters describing the eligibility criteria*	245 / 1437
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	102	*Number of patients (females)*	306
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.37 (0.56)	*Mean pre-trial ARR (SD)*	1.447 (0.684)
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.5 (1.1)	*Mean score on the EDSS (SD)*	2.367 (1.067)
Median score on the (IQR)	2	*Median score on the (IQR)*	-

study ID #41

Fazekas et al. 2008

General information

Title	Intravenous immunoglobulin in relapsing-remitting multiple sclerosis: a dose-finding trial		
Authors	Fazekas F, Lublin FD, Li D, Freedman MS, Hartung HP, Rieckmann P, Sørensen PS, Maas-Enriquez M, Sommerauer B, Hanna K; PRIVIG Study Group; UBC MS/MRI Research Group		
Date of publication	Jul 2008	*Journal / Reference*	Neurology 71 (4): 265-71
Score on the OQS	5		
Definition of MS	McDonald 2001; Lublin 1996		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.2 g/kg/4w IVIg-C 10%; 0.4 g/kg/4w IVIg-C 10% (1:1:1)		
Trial ARR of the placebo group (SD)	0.5 (1.02)	*Number of patients considered for calculation of trial ARR*	41
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	48 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 4.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	2	*Words / characters describing the eligibility criteria*	83 / 430
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	41	*Number of patients (females)*	127 (95)
Mean age (SD) in years	33 (8.7)	*Mean age (SD) in years*	33.082 (8.038)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	2.3 (1.5)	*Mean MS duration (SD) in years*	2.606 (1.851)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1.4 (0.8)	*Mean pre-trial ARR (SD)*	1.469 (1.066)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.1 (1.2)	*Mean score on the EDSS (SD)*	1.996 (1.071)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #42

Garren et al. 2008

General information

Title	Phase 2 trial of a DNA vaccine encoding myelin basic protein for multiple sclerosis		
Authors	Garren H, Robinson WH, Krasulová E, Havrdová E, Nadj C, Selmaj K, Losy J, Nadj I, Radue EW, Kidd BA, Gianettoni J, Tersini K, Utz PJ, Valone F, Steinman L; BHT-3009 Study Group		
Date of publication	May 2008	*Journal / Reference*	Ann Neurol 63 (5): 611-20
Score on the OQS	4		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.5 mg BHT-3009; 1.5 mg BHT-3009 (1:1:1)		
Trial ARR of the placebo group (SD)	0.44	*Number of patients considered for calculation of trial ARR*	87
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	48 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 3.5
Relapse-free time before baseline	50 days	*Steroid-free time before baseline*	50 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	11	*Words / characters describing the eligibility criteria*	111 / 609
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	87 (62)	*Number of patients (females)*	267 (185)
Mean age (SD) in years	37.2	*Mean age (SD) in years*	36.499
Median age (IQR) in years	37	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	6.242	*Mean MS duration (SD) in years*	6.439
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	0.95	*Mean pre-trial ARR (SD)*	0.999
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.48	*Mean score on the EDSS (SD)*	2.449
Median score on the (IQR)	2.5	*Median score on the (IQR)*	-

study ID #43

Hauser et al. 2008

General information

Title	B-cell depletion with rituximab in relapsing-remitting multiple sclerosis		
Authors	Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, Bar-Or A, Panzara M, Sarkar N, Agarwal S, Langer-Gould A, Smith CH; HERMES Trial Group		
Date of publication	Feb 2008	*Journal / Reference*	N Engl J Med 358 (7): 676-88
Score on the OQS	4		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 1 g Rituximab (1:2)		
Trial ARR of the placebo group (SD)	0.7 (1.05)	*Number of patients considered for calculation of trial ARR*	35
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	48 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	90 / 580
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	35 (29)	*Number of patients (females)*	104 (81)
Mean age (SD) in years	41.5 (8.5)	*Mean age (SD) in years*	40.239 (8.639)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	9.6 (7.1)	*Mean MS duration (SD) in years*	9.6 (6.609)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	2.5	*Median score on the (IQR)*	-

study ID #44

Kappos et al. 2008

General information

Title	Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study		
Authors	Kappos L, Gold R, Miller DH, Macmanus DG, Havrdová E, Limmroth V, Polman CH, Schmierer K, Yousry TA, Yang M, Eraksoy M, Meluzinova E, Rektor I, Dawson KT, Sandrock AW, O'Neill GN; BG-12 Phase IIb Study Investigators		
Date of publication	Oct 2008	*Journal / Reference*	Lancet 372 (9648): 1463-72
Score on the OQS	4		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 120 mg/d Fumarat per os; 360 mg/d Fumarat per os; 720 mg/d Fumarat per os (1:1:1:1)		
Trial ARR of the placebo group (SD)	0.65 (1.193)	*Number of patients considered for calculation of trial ARR*	65
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	50 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	37	*Words / characters describing the eligibility criteria*	226 / 1387
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	65 (36)	*Number of patients (females)*	256 (164)
Mean age (SD) in years	35.6 (8.2)	*Mean age (SD) in years*	35.993 (9.266)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	6 (4; 11)	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.67 (1.23)	*Mean score on the EDSS (SD)*	2.642 (1.18)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #45

Mostert et al. 2008

General information

Title	Effects of fluoxetine on disease activity in relapsing multiple sclerosis: a double-blind, placebo-controlled, exploratory study		
Authors	Mostert JP, Admiraal-Behloul F, Hoogduin JM, Luyendijk J, Heersema DJ, van Buchem MA, De Keyser J		
Date of publication	May 2008	*Journal / Reference*	J Neurol Neurosurg Psychiatry 79 (9): 1027-31
Score on the OQS	4		
Definition of MS	McDonald 2001; Poser 1983		

Intervention

Treatment arms (Allocation ratio)	Placebo; 20 mg/d Fluoxetine (1:1)		
Trial ARR of the placebo group (SD)	0.687	*Number of patients considered for calculation of trial ARR*	19
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	8 weeks
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	Complex
Number of eligibility criteria	15	*Words / characters describing the eligibility criteria*	124 / 708
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	19 (10)	*Number of patients (females)*	38 (20)
Mean age (SD) in years	38 (9)	*Mean age (SD) in years*	39.5 (9.506)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	11 (8)	*Mean MS duration (SD) in years*	11 (7.414)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	3	*Median score on the (IQR)*	-

study ID #46

Segal et al. 2008

General information

Title	Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study		
Authors	Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH; Ustekinumab MS Investigators		
Date of publication	Sep 2008	*Journal / Reference*	Lancet Neurol 7 (9): 796-804
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 27 mg/4w Ustekinumab; 90 mg/8w Ustekinumab; 90 mg/4w Ustekinumab; 180 mg/4w Ustekinumab (1:1:1:1:1)		
Trial ARR of the placebo group (SD)	0.374	*Number of patients considered for calculation of trial ARR*	49
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	37 weeks

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	1 month	*Steroid-free time before baseline*	1 month
Minimum pre-trial ARR	Complex	*Time considered for calculation of pre-trial ARR in years*	complex
Number of eligibility criteria	15	*Words / characters describing the eligibility criteria*	121 / 690
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	49 (37)	*Number of patients (females)*	249 (175)
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	34	*Median age (IQR) in years*	38
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	1.9	*Median MS duration (IQR) in years*	1.9
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	2.5	*Median score on the (IQR)*	2.5

study ID #47

Barkhof et al. 2010

General information

Title	Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant?		
Authors	Barkhof F, Hulst HE, Drulović J, Uitdehaag BM, Matsuda K, Landin R; MN166-001 Investigators		
Date of publication	Mar 2010	*Journal / Reference*	Neurology 74 (13): 1033-40
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 30 mg/d Ibudilast; 60 mg/d Ibudilast (1:1:1)		
Trial ARR of the placebo group (SD)	0.9 (1)	*Number of patients considered for calculation of trial ARR*	90
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	1 year

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	45 days
Minimum pre-trial ARR	-	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	19	*Words / characters describing the eligibility criteria*	134 / 895
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	100 (66)	*Number of patients (females)*	292 (1.95)
Mean age (SD) in years	35.7 (8.8)	*Mean age (SD) in years*	35.803 (9.139)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	4.7 (2.2; 9)	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.3 (1.2)	*Mean score on the EDSS (SD)*	3.334 (1.263)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #48

Giovannoni et al. 2010

General information

Title	A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis		
Authors	Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, Vermersch P, Chang P, Hamlett A, Musch B, Greenberg SJ; CLARITY Study Group		
Date of publication	Jan 2010	*Journal / Reference*	N Engl J Med 362 (5): 416-26
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 3.5 mg/kg/96w Cladribine; 5.25 mg/kg/96w Cladribine (1:1:1)		
Trial ARR of the placebo group (SD)	0.33 (0.48)	*Number of patients considered for calculation of trial ARR*	437
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	96 weeks

Eligibility criteria

Age	-	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	16	*Words / characters describing the eligibility criteria*	199 / 1083
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	437 (288)	*Number of patients (females)*	1326 (898)
Mean age (SD) in years	38.7 (9.9)	*Mean age (SD) in years*	38.576 (10.037)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.9 (7.4)	*Mean MS duration (SD) in years*	8.711 (7.423)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.9 (1.3)	*Mean score on the EDSS (SD)*	2.902 (1.306)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #49

Kappos et al. 2010

General information

Title	A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis		
Authors	Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P; FREEDOMS Study Group		
Date of publication	Jan 2010	*Journal / Reference*	N Engl J Med 362 (5): 387-40
Score on the OQS	5		
Definition of MS	Polman 2005		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.5 mg/d Fingolimod; 1.25 mg/d Fingolimod (1:1:1)		
Trial ARR of the placebo group (SD)	0.4 (0.678)	*Number of patients considered for calculation of trial ARR*	418
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	complex
Number of eligibility criteria	14	*Words / characters describing the eligibility criteria*	114 / 647
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	418 (298)	*Number of patients (females)*	1272 (889)
Mean age (SD) in years	37.2 (8.6)	*Mean age (SD) in years*	37.068 (8.767)
Median age (IQR) in years	37	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.1 (6.4)	*Mean MS duration (SD) in years*	8.167 (6.634)
Median MS duration (IQR) in years	7	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.5 (0.8) 2 year period: 1.1 (0.6)	*Mean pre-trial ARR (SD)*	1 year period: 1.467 (0.769) 2 year period: 1.067 (0.601)
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.5 (1.3)	*Mean score on the EDSS (SD)*	2.4 (1.336)
Median score on the (IQR)	2	*Median score on the (IQR)*	-

study ID #50

Vollmer et al. 2010

General information

Title	A phase 2, 24-week, randomized, placebo-controlled, double-blind study examining the efficacy and safety of an anti-interleukin-12 and -23 monoclonal antibody in patients with relapsing-remitting or secondary progressive multiple sclerosis		
Authors	Vollmer TL, Wynn DR, Alam MS, Valdes J		
Date of publication	Dec 2010	*Journal / Reference*	Mult Scler 17 (2): 181-91
Score on the OQS	4		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; 200 mg/2w s.c. ABT-874 s.c.; 200 mg/w s.c. ABT-874 (1:1:1)		
Trial ARR of the placebo group (SD)	0.5 (1.271)	*Number of patients considered for calculation of trial ARR*	69
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 6.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	4 weeks
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	1
Number of eligibility criteria	13	*Words / characters describing the eligibility criteria*	129 / 785
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	69 (47)	*Number of patients (females)*	215 (153)
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	44	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.5 (7.6)	*Mean MS duration (SD) in years*	8.179 (7.145)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.4 (1.5)	*Mean score on the EDSS (SD)*	3.332 (1.632)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #51

De Stefano et al. 2011

General information

Title	Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: further outcomes from the IMPROVE study.		
Authors	De Stefano N, Sormani MP, Stubinski B, Blevins G, Drulović JS, Issard D, Shotekov P, Gasperini C		
Date of publication	Aug 2011	*Journal / Reference*	J Neurol Sci 312 (1-2): 97-101
Score on the OQS	2		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; Interferon beta-1a 44 µg 3x/w (1:2)		
Trial ARR of the placebo group (SD)	1.076 (1.933)	*Number of patients considered for calculation of trial ARR*	60
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	16 weeks

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	-	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	2	*Time considered for calculation of pre-trial ARR in years*	0.5
Number of eligibility criteria	5	*Words / characters describing the eligibility criteria*	47 / 239
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	180	*Number of patients (females)*	60
Mean age (SD) in years	-	*Mean age (SD) in years*	-
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	-	*Mean score on the EDSS (SD)*	-
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #52

Kappos et al. 2011

General information

Title	Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial		
Authors	Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, Yin M, Leppert D, Glanzman R, Tinbergen J, Hauser SL		
Date of publication	Nov 2011	*Journal / Reference*	Lancet. 378 (9805): 1779-87
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	2x Placebo; 2x Ocrelizumab 600 mg; 2x Ocrelizumab 2000 mg; Inferferon beta-1a 30 µg 1x/w (1:1:1:1)		
Trial ARR of the placebo group (SD)	0.64 (0.956)	*Number of patients considered for calculation of trial ARR*	54
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	1 – 6
Relapse-free time before baseline	-	*Steroid-free time before baseline*	28 days
Minimum pre-trial ARR	0.667	*Time considered for calculation of pre-trial ARR in years*	3
Number of eligibility criteria	19	*Words / characters describing the eligibility criteria*	152 / 910
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	54 (36	*Number of patients (females)*	218 (141)
Mean age (SD) in years	38 (8.8)	*Mean age (SD) in years*	37.545 (8.841)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	-	*Mean MS duration (SD) in years*	-
Median MS duration (IQR) in years	4.8	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	-	*Mean pre-trial ARR (SD)*	-
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	3.2 (1.4)	*Mean score on the EDSS (SD)*	3.301 (1.426)
Median score on the (IQR)	3	*Median score on the (IQR)*	-

study ID #53

O'Connor et al. 2011

General information

Title	Randomized trial of oral teriflunomide for relapsing multiple sclerosis.		
Authors	O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, Truffinet P, Wang L, Miller A, Freedman MS; TEMSO Trial Group		
Date of publication	Oct 2011	*Journal / Reference*	N Engl J Med 365 (14): 1293-303
Score on the OQS	5		
Definition of MS	McDonald 2001		

Intervention

Treatment arms (Allocation ratio)	Placebo; Teriflunomide 7 mg/d; Teriflunomide 14 mg/d (1:1:1)		
Trial ARR of the placebo group (SD)	0.54 (0.729)	*Number of patients considered for calculation of trial ARR*	363
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	108 weeks

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	60 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	71	*Words / characters describing the eligibility criteria*	589 / 3598
Eligible courses of MS	RRMS + SPMS + PRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	363 (275)	*Number of patients (females)*	1088 (785)
Mean age (SD) in years	38.4 (9)	*Mean age (SD) in years*	37.866 (8.746)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.6 (7.1)	*Mean MS duration (SD) in years*	8.7 (6.86)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.4 (0.7) 2 year period: 1.1 (0.5)	*Mean pre-trial ARR (SD)*	1 year period: 1.367 (0.701) 2 year period: 1.117 (0.536)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.68 (1.34)	*Mean score on the EDSS (SD)*	2.677 (1.307)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #54

Comi et al. 2012

General information

Title	Placebo-Controlled Trial of Oral Laquinimod for Multiple Sclerosis		
Authors	Comi G, Douglas J, Kappos L, Montalban X, Boyko A, Rocca MA, Filippi M		
Date of publication	Mar 2012	*Journal / Reference*	N Engl J Med 366 (11): 1000-9
Score on the OQS	5		
Definition of MS	Polman 2005		

Intervention

Treatment arms (Allocation ratio)	Placebo; 0.6 mg/d Laquinimod (1:1)		
Trial ARR of the placebo group (SD)	0.39 (0.707)	*Number of patients considered for calculation of trial ARR*	556
Primary outcome	Relapse-related	*Duration of placebo-controlled follow-up*	2 years

Eligibility criteria

Age	18 – 55	*Score on the EDSS*	0 – 5.5
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	complex
Number of eligibility criteria	57	*Words / characters describing the eligibility criteria*	609 / 3529
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	556 (368)	*Number of patients (females)*	1106 (759)
Mean age (SD) in years	38.5 (9.1)	*Mean age (SD) in years*	38.699 (9.148)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.7 (6.7)	*Mean MS duration (SD) in years*	8.7 (6.797)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.3 (0.7) 2 year period: 0.95 (0.5)	*Mean pre-trial ARR (SD)*	1 year period: 1.25 (0.702) 2 year period: 0.95 (0.5)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.6 (1.3)	*Mean score on the EDSS (SD)*	2.6 (1.299)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #55

Miller et al. 2012

General information

Title	Firategrast for relapsing remitting multiple sclerosis: a phase 2, randomised, double-blind, placebo-controlled trial		
Authors	Miller DH, Weber T, Grove R, Wardell C, Horrigan J, Graff O, Atkinson G, Dua P, Yousry T, Macmanus D, Montalban X		
Date of publication	Jan 2012	*Journal / Reference*	Lancet Neurol 11 (2): 131-9
Score on the OQS	5		
Definition of MS	Polman 2005		

Intervention

Treatment arms (Allocation ratio)	Placebo; Firategrast 150 mg 2x/d; Firategrast 600 mg 2x/d; Firategrast 900 mg 2x/d; Firategrast 1200 mg 2x/d; (2:1:2:2)		
Trial ARR of the placebo group (SD)	0.891	*Number of patients considered for calculation of trial ARR*	99
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	24 weeks

Eligibility criteria

Age	18 – 65	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	4 weeks	*Steroid-free time before baseline*	-
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	2
Number of eligibility criteria	15	*Words / characters describing the eligibility criteria*	171 / 916
Eligible courses of MS	RRMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	99 (66)	*Number of patients (females)*	343 (230)
Mean age (SD) in years	39 (11)	*Mean age (SD) in years*	39.297 (10.762)
Median age (IQR) in years	-	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	5.5 (5.9)	*Mean MS duration (SD) in years*	5.85 (5.916)
Median MS duration (IQR) in years	-	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.7 (0.7) 2 year period: 1.35 (0.485)	*Mean pre-trial ARR (SD)*	1 year period: 1.616 (0.724) 2 year period: 1.272 (0.475)
Median pre-trial ARR (IQR)	-	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.7 (1.4)	*Mean score on the EDSS (SD)*	2.786 (1.375)
Median score on the (IQR)	-	*Median score on the (IQR)*	-

study ID #56

Saida et al. 2012

General information

Title	A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis		
Authors	Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, Tang D, Zhang-Auberson L, Kira J		
Date of publication	Feb 2012	*Journal / Reference*	Mult Scler 18 (9): 1269-77
Score on the OQS	5		
Definition of MS	Polman 2005		

Intervention

Treatment arms (Allocation ratio)	Placebo; Fingolimod 0.5 mg/d; Fingolimod 1.25 mg/d (1:1:1)		
Trial ARR of the placebo group (SD)	0.99 (1.435)	*Number of patients considered for calculation of trial ARR*	57
Primary outcome	MRI-related	*Duration of placebo-controlled follow-up*	6 months

Eligibility criteria

Age	18 – 60	*Score on the EDSS*	0 – 6
Relapse-free time before baseline	30 days	*Steroid-free time before baseline*	30 days
Minimum pre-trial ARR	1	*Time considered for calculation of pre-trial ARR in years*	-
Number of eligibility criteria	44	*Words / characters describing the eligibility criteria*	390 / 2262
Eligible courses of MS	RRMS + SPMS		

Patient characteristics at baseline (placebo group)		**Patient characteristics at baseline (all groups)**	
Number of patients (females)	57 (39)	*Number of patients (females)*	171 (118)
Mean age (SD) in years	35 (8.9)	*Mean age (SD) in years*	35.333 (9.027)
Median age (IQR) in years	34	*Median age (IQR) in years*	-
Mean MS duration (SD) in years	8.2 (7.3)	*Mean MS duration (SD) in years*	7.833 (6.505)
Median MS duration (IQR) in years	6	*Median MS duration (IQR) in years*	-
Mean pre-trial ARR (SD)	1 year period: 1.7 (1.6) 2 year period: 1.4 (1.5)	*Mean pre-trial ARR (SD)*	1 year period: 1.533 (1.206) 2 year period: 1.217 (1.076)
Median pre-trial ARR (IQR)	1	*Median pre-trial ARR (IQR)*	-
Mean score on the EDSS (SD)	2.1 (1.7)	*Mean score on the EDSS (SD)*	2.067 (1.771)
Median score on the (IQR)	2	*Median score on the (IQR)*	-