Over three decades study populations in progressive multiple sclerosis have become older and more disabled, but have lower on-trial progression rates: a systematic review and meta-analysis of 43 randomized placebo-controlled trials

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Abstract

**Background:** Progression is the major driver of disability and cost in multiple sclerosis (MS). However, the search for treatments in progressive MS (PMS) has not mirrored the success in relapsing MS.

**Objectives:** To assess changes in PMS trials over time.

**Methods:** Pubmed, Medline and Embase were searched to identify randomised, double blind, placebo-controlled trials in PMS. PRISMA guidelines were used, study quality assessed and trends examined by regressions.

**Results:** Placebo groups of 43 studies published between 1988 and 2018 were included. The mean age at trial entry increased by 9.8 years per decade (95% CI [2.7; 4.9], p<.001). Mean baseline EDSS scores increased by 0.36 points ([0.09; 0.62], p=0.009) and disease durations at baseline were prolonged by 1.8 years ([0.7; 2.9]; p=0.003) per decade. The trials became larger, specifically placebo groups increased by about 222 patients ([36; 409]; p=0.021) and 88 patients ([12; 165]; p=0.025) per decade for PPMS and SPMS, respectively. The proportion of patients on placebo experiencing disability progression within 24 months decreased by 7.6 percentage points ([1.2; 14.1], p=0.022) per year.

**Conclusions:** Over three decades PMS trial populations changed and are now older, with a longer disease duration and more disability, with lower on-trial progression rates.
Introduction

Multiple sclerosis (MS) is the most common cause of disability in younger adults with the majority of its impact arising from permanent irreversible disability as progression develops and evolves (1; 2; 3). Relapsing MS is the presentation in 85% of people with MS due to episodes of transient neurological deterioration, being the dominant feature. However, 15% develop insidious disability progression from onset with no relapses, termed primary progressive (PP)MS. In addition relapsing onset MS converts to secondary progressive (SP)MS at a rate of 2-3% of per year with a median time to secondary progression ranging from 15-21.4 years from onset (4-8). There is debate as to whether these are separate or continuous entities (9-11). Given its impact, progression has been a primary target of trials over many years (12). But despite some partial and incomplete success in individual studies (13,14) these trials have not led to a licensed therapy until 2017 when ocrelizumab received a FDA license for PPMS (15). In contrast, in relapsing MS over the last twenty years, at least ten treatments have emerged. This evolution of treatment has impacted on the placebo population taking part in relapsing MS trials, with reductions in annualized relapse rates from about 1.5 to less than 0.5 over two decades (16). Whereas changing trial populations are well documented in relapsing MS (16-20), this has not been systematically studied for progressive MS. Here we performed a systematic review to identify randomised placebo-controlled trials in progressive MS to determine whether the trial populations have changed over time (21).
Methods

Our systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (22).

Systematic literature search

A systematic literature search (last search conducted June 12th, 2017) of Pubmed, Medline and Embase was conducted without date restrictions to identify placebo-controlled, double-blind randomized controlled trials in MS where all or some of the patients had a progressive form of the disease. In terms of the PICOS scheme (with PICOS referring to population, intervention, control, outcome and study design) the target population was progressive MS of any type, the intervention was any pharmacological intervention, the control was placebo, the outcomes of the review included baseline characteristics of the trials and EDSS assessed disease worsening and study design was randomized placebo-controlled trial with parallel treatment arms. Specifically, the search terms were (‘progressive' OR 'progression') AND 'multiple sclerosis' AND 'trial'. Three articles were obtained from expert discussion (23-25). Out of these one trial was published only as a book chapter (23), one as an abstract (24) and for one only top line results are available from clinicaltrials.gov (25). As the publication of the latter appeared during the course of the revision of this manuscript, the records were updated accordingly. All abstracts were independently screened by two reviewers (EH, RN). If one reviewer suggested that the full paper should be examined after reading the abstract, the full paper was obtained. For a trial to be included it had to be randomised, double blind, and placebo-controlled (including add-on placebo control), with at least some of the trial participants having PMS which were separately reported. Trials had to assess the efficacy of disease modifying drugs (i.e. not assessing symptomatic therapies), and report data on expanded disability status scale (EDSS). We excluded cross-over trials.
Data extraction

The following data were extracted by one reviewer (EH) using a prespecified spreadsheet and verified by two others (RN, TF):

- Publication: first author, year of publication;
- Baseline characteristics of the placebo group patients: numbers of patients, mean age, percentage (%) of female subjects, mean EDSS, % primary progressive MS and duration of their follow-up;
- Eligibility criteria: lower and upper bounds on age and EDSS;
- Outcome data of the placebo group patients: proportion of placebo patients exhibiting a worsening in EDSS at 24 months. This could have been defined by current standard criteria or just as worsening

Baseline was taken as time point of either study entry or randomization; publications often do not distinguish between these two. We did not extract baseline data for the total trial population as this study focused on the outcomes of the placebo groups. Therefore, to be consistent only baseline data of the placebo control group was considered.

If means were not available but medians were, these were used. The proportions of patients with worsening in EDSS over 24 months were extracted from tabulated data or Kaplan-Meier curves.

Quality assessment

Cochrane risk of bias tool (26) assessing the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participant and personnel (performance bias), outcome assessment (detection bias), incomplete outcome data
(attrition bias), selective reporting (reporting bias). All items were scored on a three point scale (low, unclear and high risk of bias) by two reviewers (EH, JR) and any disagreements were resolved by discussion between reviewers. A third reviewer (RN) was consulted if any disagreements remained.

**Statistical analyses**

The distributions of basic demographics and clinical characteristics of the placebo group participants were summarized by mean, standard deviation, median, minimum and maximum. Changes in placebo trial populations and trial characteristics over time were investigated by linear regression models with characteristic of interest as the dependent variable and publication year as well as the population phenotype (i.e. pure PPMS, pure SPMS, or mixed PPMS/SPMS study populations) as the independent variable. If the population phenotype was statistically significant on a 5% level, then an interaction between the populations phenotype and publication year was assessed. Similarly, the percentage of patients progressing within 24 months from randomization were modelled depending on publication year. The fitted regression lines were added with pointwise 95% confidence bands to the scatter plots. The regression coefficients are reported with 95% confidence intervals and p-values testing the null hypothesis of the regression coefficient being equal to zero. Standard diagnostics were used to assess model fit. As a supporting analysis, a meta-regression was conducted for the proportion of patients progressing within 24 months from randomization. Here we followed an approach similar to the one taken in (20). Changes in eligibility criteria over time were investigated by linear regression models with characteristic of interest as the dependent variable and publication year as the independent variable.
Furthermore, the likelihood of imposing an upper bound on EDSS was modelled by a logistic regression using the Firth correction. All analyses were carried out using SAS version 9.4.
Results

Identified trials, their baseline characteristics and rated quality

We found 43 studies published between 1988 and 2018 that fulfilled our eligibility criteria (Figure 1). The references of the studies are provided in eTable 1. The publications were fairly evenly spread across the reporting period (Figure 2) with half of the trials being published before or in 2002. Twenty-one trials (48.8%) recruited mixed phenotype populations of SPMS/PPMS, 17 trials (39.5%) a pure SPMS population and five (11.6%) a pure PPMS population. The five trials of pure PPMS populations all occurred in or after 2003 whereas the SPMS trials were more uniformly distributed over time with half of the trials being published before or in 2002. Baseline characteristics of the placebo groups are summarized in Table 1.

The quality of the trials as assessed by the Cochrane risks of bias tool was overall very good (Figure 3). However, attrition risk due to incompleteness of outcome data was rated high for 10 out of 43 studies (23%). The earlier studies often stated they were randomised, but did not state exactly what randomisation methods and allocation concealment methods were used. Fourteen out of 43 studies (33%) were considered inadequately blinded, although this was often unavoidable, for example because the active treatment had considerable side effects. The individual ratings of the studies are included as supplementary figure (eFigure 1).

Changing trial sizes with time

Notably the trial sizes changed over time, with differences in trial sizes and changes over time between the different phenotypes (Figure 4). Specifically, PPMS and SPMS trials increased by about 22.2 patients (95% CI [3.6; 40.9]; p=0.021) and 8.8 patients (95% CI [1.2; 16.5]; p=0.025) per calendar year in the placebo group, respectively. In contrast the trials in mixed populations were fairly stable in size (-1.2 patients per year; 95% CI [-6.0; 3.6]; p=0.611).
Changing placebo PMS populations with time

At trial entry, participants were older in more recent studies (Figure 5A). Adjusted for population phenotype (i.e. pure PPMS, pure SPMS, or mixed PPMS/SPMS study populations) the mean baseline age increased by 0.38 years per calendar year (95% CI [0.27; 0.49]; p<0.001), or 11.4 years (95% CI [8.1; 14.7]) over the 30 years considered in this review. In this model the differences between the population phenotypes in terms of baseline mean age were not statistically significant (p=0.761), with pure PPMS populations and pure SPMS populations being on average 1.1 years (95% CI [-2.0; 4.3]) and 0.4 years (95% CI [-1.6; 2.3]) younger than mixed populations. Therefore, we did not test for interactions of baseline age with publication year. Entry disability showed an increase over time (Figure 5B). Adjusted for population phenotype, mean entry EDSS scores increased by 0.03561 points per calendar year (95% CI [0.0094; 0.0618]; p=0.009), or 1.1 points (95% CI [0.28; 1.85]) over the period considered in this review. A trend towards lower mean EDSS at baseline was noted in the PPMS study populations as compared to SPMS populations (difference of 0.77, 95% CI [0.03; 1.51], p=0.042) and mixed populations (difference of 0.90, 95% CI [0.15, 1.66], p=0.020), although the factor was not statistically significant overall (p=0.063). Over time mean disease durations lengthened (Figure 5C). The disease durations were 0.177 year greater per calendar year (95% CI [0.066; 0.287]; p=0.0025) or 5.3 years (95% CI [2.0; 8.6]) over this period, adjusted for population phenotype. In this model the PPMS population had significantly shorter disease durations compared to SPMS (difference of 6.78 years, 95%CI [3.77; 9.78], p<0.001) and mixed populations (difference of 5.64 years, 95% CI [2.56; 8.72], p<0.001). However, the interaction between population phenotype and publication year was not significant (p=0.077) and therefore not considered further. Adjusted for populations phenotype, there were no statistically significant changes in the percentage of females
enrolled (p=0.373). However, there were differences in the sex distributions across the different phenotypes (p=0.001), with fewer females in the pure PPMS populations as compared to mixed populations and more females in the pure SPMS populations as compared to the mixed populations.

**Changing eligibility criteria with time**

Given the changes in placebo PMS populations with time, we investigated whether there were changes in the eligibility criteria, specifically age and EDSS criteria, over time. For age we did not observe any changes in the lower bound (n=33, 0.03 years per calendar year, 95% CI (-0.09; 0.15), p= 0.588) whereas the upper bound increased by 0.34 years per calendar year (n=33, 95% CI [0.14; 0.54], p=0.001) (Figure 6). There was no statistically significant interaction with disease phenotype. For EDSS we observed that where quoted the upper bound did not change with time (n=39, 0.005 points per calendar year, 95% CI [-0.014; 0.024], p=0.589). However, there were some changes over time with regard to the lower bound. Later trials were more likely to define a lower bound than earlier trials (n=43, OR= 1.30 per calendar year, 95% CI [1.11; 1.53], p=0.001). This is illustrated in Table 2. It is notable that all pure PPMS trials (n=5) used lower bounds; these varied between 2 and 3.5 on the EDSS.

**On trial disability accumulation in placebo subjects is changing**

We identified 28 publications that reported 24 months disability progression probabilities. A number of definitions were used by different studies (Table 3). The proportion of placebo participants experiencing 24 month disability progression as defined in each study decreased by 0.76 percentage points per calendar year (95% CI [0.12; 1.41]; p=0.022; Figure 7). This amounts to a decrease of 23 percentage points (95% CI [4; 42]) over the 30 year study period.
Adjusting for population phenotype did not improve model fit as numbers were small (mixed populations n=13, SPMS n=10, PPMS n=5). Considering the subgroup of trials using a similar definition of progression (n=12) we found similar trends over time as in the larger group. Specifically, the proportion of placebo participants experiencing 24 month disability progression decreased by 0.79 percentage points per calendar year (95% CI [0.24; 1.35]; p=0.009).

Further analyses using meta-regression allowing for between-trial heterogeneity in the placebo responses confirmed our findings (OR=0.717 per decade, 95% CI [0.541, 0.951]; p=0.022; between-trial variance 0.33). In the subgroup of the 12 trials the meta-regression resulted in an OR=0.752 per decade (95% CI [0.535 1.057]; p=0.092; between-trial variance 0.07).
Discussion

This work has demonstrated that placebo trial populations in PMS trials have evolved over three decades, mirroring changes in RMS placebo trial populations (19). There is increased interest in PMS trials given the recent licensing of ocrelizumab (27). Given the relative failure of drug development pathways in PMS compared to RMS it is important to try and identify features of PMS that may allow us to maximise the chance of success in future PMS trials.

This systematic review and meta-analysis in PMS identified 43 randomized placebo-controlled trials completed over a period of 28 years. Similar to prior systematic reviews in RMS (16-20) we found that the trial populations have changed over time. Here we show that the PMS placebo populations are getting older with a longer disease duration and more disability on trial entry. In part this could be explained by changing eligibility criteria notably the introduction of a lower bound EDSS to define progression (28). This will have the effect of increasing both age, disease duration and disability at entry. In addition as has been surmised (29) the enrolled populations have progressed less in more recent trials as reflected in lower on-trial progression probabilities. Reflecting this evolution over time we find that the trial sizes are increasing in the mono-phenotypic populations.

A recently published trial by Kappos et al. (30) confirms some of our findings. Firstly, the primary endpoint uses the disease progression definition found to be most common in our systematic review. Secondly, the probability of confirmed disease progression in the placebo group at 24 months was very similar to the values predicted by both analysis models employed here. Thirdly, the baseline characteristics such as age, sex, EDSS and disease duration were typical for SPMS trials included in this review.

Although definitions of EDSS progression vary across trials, in 23 out of 28 studies progression was confirmed after at least 3 months. There is no general agreement on the length of the
confirmation period assessing disability progression in PMS, it has been cited in earlier
definitions as needing to be confirmed at a year (31) and European regulators have a
preference for 6 months confirmed disability worsening (32). One notable finding was the
introduction of the eligibility criteria that included a lower bound EDSS of 2 to 3.5 that forms
part of the definition of progression (28). This has arisen from our understanding of when
progression in MS is thought to be evident in SPMS, although by definition progression in
PPMS will be present at the onset when the EDSS is very low. This change in part has been
driven by the availability of treatment for RMS. Furthermore, treatment for RMS is also
thought to underpin the reduction in the diagnoses of PPMS (33,34).

In standard meta-analysis estimating treatment effects across trials, assigning higher weight
to more informative, often larger studies is a very sensible approach. Here we are looking at
time trends. With the more recent studies being larger assigning higher weights to the larger
studies risks exaggerating the time effect. For continuous characteristics such as mean age at
baseline or mean EDSS at baseline the level of information contained does not only depend
on the sample size of the study but also on the variance of the particular characteristic. The
conduct and reporting of clinical trials has changed considerably over the past decades.
Although we found that reporting of the main aspects were sufficiently consistent to warrant
integrated analyses, the reporting of peripheral features such as dispersion measures was
variable. How to deal with missing measures of dispersion in meta-analyses is subject to
ongoing methodological research (35). Therefore, we opted for this systematic review to use
simpler and easier to interpret analyses techniques. For the primary endpoint probability of
disease progression over 24 months, additional meta-regression analyses were conducted
confirming the results of the primary analyses, which also provides some reassurance in the
robustness of the other analyses.
Given the changes in trial conduct and design since 1988 the overall quality of the trials was high with increasing trial sizes in common with RMS studies (36). But unlike development programs in RMS this has not produced a range of treatment options. This could be due to several reasons. One is the lack of a phase 2 surrogate outcome that allows early decision making in drug development (37). This, together with an emerging understanding of the underlying pathology of progression will allow the wrong compounds to enter confirmatory trials. Secondly, it could be due to targeting the wrong target population. Recent trials have focused on monophenotypic disease but there remains an ongoing discussion about the similarity and differences between the progression seen in PPMS and SPMS (9-11).

There is likely to be an impact on PMS trials over the period of this systematic review with the widespread uptake of treatments for relapsing MS. In particular as seems likely here this will modify the population entering PMS trials. In the early years of this review there were no treatments for either RMS or PMS thus being in a trial was the only opportunity to access a therapy. Subsequently the availability of treatments will result in those transitioning to PMS and those with a relapsing progressive course likely be offered RMS therapy and will not take part in PMS trials. Removing subjects in relapse may in fact slow the progression rate as EDSS progression up to 3 months is still influenced by relapses. As a result a progression rate in purer PMS population might be more indicative of actual true progression and consequently differences between groups might be easier to detect. Ocrelizumab recently licensed in PMS has shown a 20% slowing of progression rates but the population was enriched with inflammatory subjects e.g. Gadolinium enhancement (15). In clinical practice, it is unclear how meaningful this effect is given the long-term nature of the condition. Purposely not enrolling those with inflammatory MS in a given trial might enhance ability to identify a treatment effective in PMS targeting neurodegeneration. This may have occurred in the simvastatin
phase 2 trial where both the primary as well as a number of secondary outcomes were positive (38).

Given the partial impact of anti-inflammatory therapies thus far in PMS, targeting the neurodegenerative component is vitally important to allow us to improve therapy as a whole for this debilitating condition. Targeting mature PMS populations together with improvements in trial design that have been used successfully in the recent phase 3 trials in PMS (15) as well as improvements in outcome measures in both in phase 2 and 3 trials will hopefully streamline the testing of novel molecules.


9. Tremlett H, Zhao Y. Primary and secondary progressive MS have a similar age at onset of progression - NO. *Mult Scler.* 2017; 23(5): 640-642.
10. Vukusic S. Primary and secondary progressive MS have a similar age at onset of progression – YES. *Mult Scler.* 2017;23(5):638–639.


19. Steinvorth SM, Röver C, Schneider S, Nicholas R, Straube S, Friede T. Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in


Table 1. Basic demographics and clinical characteristics of the placebo group participants.

<table>
<thead>
<tr>
<th>Population</th>
<th>Characteristic</th>
<th>No. of studies</th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Mean number</td>
<td>43</td>
<td>118.7 (127.6)</td>
<td>55.0 (8.0, 487.0)</td>
</tr>
<tr>
<td></td>
<td>Mean Age (years)</td>
<td>43</td>
<td>45.1 (4.3)</td>
<td>46.0 (33.4, 52.0)</td>
</tr>
<tr>
<td></td>
<td>% women</td>
<td>41</td>
<td>56.8 (10.8)</td>
<td>58.5 (25.0, 80.0)</td>
</tr>
<tr>
<td></td>
<td>Mean EDSS</td>
<td>43</td>
<td>5.2 (0.8)</td>
<td>5.2 (3.1, 6.5)</td>
</tr>
<tr>
<td></td>
<td>MS Duration (years)</td>
<td>40</td>
<td>12.0 (3.5)</td>
<td>11.9 (5.9, 20.3)</td>
</tr>
<tr>
<td>SPMS</td>
<td>Mean number</td>
<td>17</td>
<td>146.1 (140.6)</td>
<td>70.0 (8.0, 448.0)</td>
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<tr>
<td></td>
<td>Mean Age (years)</td>
<td>17</td>
<td>45.3 (4.1)</td>
<td>45.0 (38.8, 51.2)</td>
</tr>
<tr>
<td></td>
<td>% women</td>
<td>17</td>
<td>62.7 (9.9)</td>
<td>61.2 (46.7, 80.0)</td>
</tr>
<tr>
<td></td>
<td>Mean EDSS</td>
<td>17</td>
<td>5.2 (0.7)</td>
<td>5.2 (3.7, 6.5)</td>
</tr>
<tr>
<td></td>
<td>MS Duration (years)</td>
<td>16</td>
<td>13.5 (3.6)</td>
<td>13.9 (7.1, 20.3)</td>
</tr>
<tr>
<td>PPMS</td>
<td>Mean number</td>
<td>5</td>
<td>242.8 (175.9)</td>
<td>244.0 (20.0, 487.0)</td>
</tr>
<tr>
<td></td>
<td>Mean Age (years)</td>
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<td>47.1 (3.2)</td>
<td>48.5 (43.0, 50.2)</td>
</tr>
<tr>
<td></td>
<td>% women</td>
<td>5</td>
<td>45.4 (11.8)</td>
<td>48.1 (25.0, 55.1)</td>
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<tr>
<td></td>
<td>Mean EDSS</td>
<td>5</td>
<td>4.7 (0.1)</td>
<td>4.7 (4.5, 4.9)</td>
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<tr>
<td></td>
<td>MS Duration (years)</td>
<td>5</td>
<td>7.9 (2.0)</td>
<td>8.0 (5.9, 10.7)</td>
</tr>
</tbody>
</table>

SD: standard deviation. Mean EDSS: In 4 out of 43 studies the mean was not available and was replaced by the median.

Table 2. The number of trials with an EDSS lower bound eligibility criteria and the EDSS range (minimum-maximum) for those with a lower boundary stratified by decade and disease phenotype

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SPMS</td>
<td>0/2</td>
<td>9/11</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>3-5</td>
<td>3-4</td>
</tr>
<tr>
<td>Mixed</td>
<td>3/11</td>
<td>3/3</td>
<td>7/7</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>3-3</td>
<td>2-4.5</td>
</tr>
<tr>
<td>PPMS</td>
<td>0/0</td>
<td>1/1</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2</td>
<td>2-3.5</td>
</tr>
<tr>
<td>Total</td>
<td>3/13</td>
<td>13/15</td>
<td>15/15</td>
</tr>
</tbody>
</table>

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Table 3. Definitions of EDSS progression used in the 28 PMS trials where data could be extracted. “Collapsed” EDSS refers to EDSS scores with scores of 3.0 to 5.5 (inclusive) assigned a grade of 5.5 (39).

<table>
<thead>
<tr>
<th>Definition of EDSS worsening</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse by 0.5 unit if baseline &gt;5, 1 units if baseline ≤5, 3 month confirmed</td>
<td>12</td>
</tr>
<tr>
<td>Worse by 0.5 unit if baseline &gt;5, 1 units if baseline ≤5, 6 month confirmed</td>
<td>5</td>
</tr>
<tr>
<td>Worse by 0.5 unit if baseline ≥6, 1 units if baseline &lt;6, 6 month confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worse by 0.5 unit if baseline &gt;5, 1 units if baseline ≤5, 4 month confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worse by 0.5 unit if baseline ≥6, 1 units if baseline &lt;6, 3 month confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worse by 1 unit if baseline ≥5, 1.5 units if baseline &lt;5, 3 month confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worsening by 1 point, 6 months confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worse by 1 point, 3 month confirmed</td>
<td>1</td>
</tr>
<tr>
<td>Worse as compared to baseline</td>
<td>4</td>
</tr>
<tr>
<td>Sustained increase of 0.5 in &quot;collapsed” EDSS</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure Legend

Figure 1. PRISMA flow diagram describing systematic literature search and study selection

Figure 2. Number of trials by epoch and phenotype (pure SPMS, mixed SPMS/PPMS, and pure PPMS)

Figure 3. Quality assessment of the n=43 trials using the Cochrane risk of bias tool

Figure 4: Number of placebo patients by phenotype (pure SPMS, mixed SPMS/PPMS, and pure PPMS) depending on year of publication (n=43). The lines give the fitted trends and the shaded areas the 95% confidence intervals.

Figure 5. Patient baseline characteristics of the placebo patients depending on year of publication: (A) mean age; (B) mean EDSS; and (C) mean disease duration. The solid lines give the fitted trends and the shaded areas the 95% confidence intervals.

Figure 6. Changes in eligibility criterion age (in years) depending on year of publication. The solid lines give the fitted trends and the dashed lines the 95% confidence intervals.

Figure 7. Percentage of placebo patients with progression within 24 months depending on year of publication (n=28). The solid line gives the fitted trend, the shaded area the 95% confidence intervals and the dashed lines the 95% prediction intervals.
Figure 1

Records identified through database searching (n=1974)

Additional records identified through other sources (n=3)

Records after duplicates removed (n=1523)

Records screened (n=1523)  Records excluded (n=1221)

Full-text articles assessed for eligibility (n=84)

Studies included in quantitative synthesis (meta-analysis) (n=43)

Full-text articles excluded (n=40)

- 2 ongoing trial/only trial protocol
- 1 study PMS data no longer available
- 1 trial contains open label phase
- 13 studies had mixed PMS and RRMS patients data
- 1 study no placebo control
- 1 study only RRMS patients
- 1 not disease-modifying therapy
- 1 study has no clinical efficacy parameters
- 19 not randomize controlled trial
Figure 5

A

Year of publication

Mean age at baseline [y]

B

Year of publication

Mean DMS at baseline

C

Year of publication

Mean disease duration at baseline [d]