Clinical trials for progressive multiple sclerosis: progress, new lessons learned, and remaining challenges

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Summary

Despite the success of disease-modifying treatments in relapsing multiple sclerosis, for many individuals living with multiple sclerosis, progressive disability continues to accrue. How to interrupt the complex pathological processes underlying progression remains a daunting and ongoing challenge. Since 2014, several immunomodulatory approaches that have modest but useful effects have been approved for the management of progressive multiple sclerosis, primarily for people who have active inflammatory disease. The approval of these drugs These **[A: these what? These approvals? The approval of these drugs? AGREED]** required large phase 3 trials that were sufficiently powered to detect meaningful effects on disability. New classes of drug, such as Bruton tyrosine-kinase inhibitors, are coming to the end of their trial stages, several candidate neuroprotective compounds have been successful in phase 2 trials and innovative approaches to remyelination are now also being explored in clinical trials. **[Or "…stages, several candidate neuroprotective compounds have been successful in phase 2 trials, and innovative approaches to remyelination are now also being explored in clinical trials"? YES]** Work continues to define intermediate outcomes that can provide results in phase 2 trials more quickly than disability measures, and more efficient trial designs, such as multi-arm multi-stage and futility approaches, are increasingly being used. Collaborations between patient organisations, pharmaceutical companies, and academic researchers will be

crucial to ensure that future trials maintain this momentum and generate results that are meaningful for people living with progressive multiple sclerosis.

Introduction [Prod: H2]

The treatment of relapsing multiple sclerosis has been transformed over the past 30 years, with the widespread use of increasingly sophisticated immunomodulatory disease-modifying treatments that principally act through modulation of peripheral immune responses.[1] Nonetheless, understanding and addressing the biology underlying the progressive stage of multiple sclerosis remains difficult. A recently proposal for a mechanistic framework for progressive multiple sclerosis[2] delineated various mechanisms that might underpin accumulation of disability and be potential intervention targets. These mechanisms **[A: mechanisms? YES]** include ongoing inflammation (comprising focal, peripherally driven neuroinflammation and, separately, chronic CNS compartmentalised inflammation), abnormal metabolic processes, oxidative stress, inadequate remyelination, and failure of compensatory mechanisms, moderated by factors such as comorbidities and age.[3] Indeed, the modest benefits seen with peripherally acting immunomodulatory disease-modifying therapies suggest they need to be augmented with therapies that address CNS inflammation, neuroprotection (to directly promote neuroaxonal integrity, independent of immunomodulation), and, ultimately, remyelination.[3]

We previously reviewed progressive multiple sclerosis from a clinical trials perspective.[4] We summarised 25 years of experience across approximately 50 phase 2b and 3 trials, collectively enrolling more than 8500 participants. Unfortunately, overall there had been little therapeutic success. Since the end of our literature search for our previous review (April 2014) **[A: or "since the end of our literature search for the previous review"? OK]** a further 22 phase 2b trials and eight phase 3 trials, which we critically review here, have reported their results, **[A: have reported their results? Correct that you are not including the ongoing studies here? YES]** including nearly 9000 additional participants. **[A: do you have exact participant numbers?8924 – I THINK BETTER TO ROUND]** We comment on issues of population choice, interim and final outcome measures, trial design, and comorbidities, and the importance of goal setting involving patient and public involvement, to ensure we address the issues most relevant to people affected by progressive multiple sclerosis. Finally, **[A: can "Finally" be omitted as ongoing trials seem to come before issues of trial design and PPI? YES]** we look forward to trials that are due to report results over the next several years, which we hope will provide a meaningful benefits for people who have progressive multiple sclerosis.

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Completed and ongoing clinical trials [Prod: H2]

In the following section, we describe randomised trials of potential therapies for progressive multiple sclerosis that have been completed (table 1) and initiated but not completed (table 2) randomised controlled trials of potential therapies for progressive multiple sclerosis **[A: can what has happened since 2014 to make these trials suitable for inclusion be clarified, eg, because a trial could have started before 2014 but be ongoing? Eg, "We describe randomised trials of potential therapies for progressive multiple sclerosis that have been**

completed (table 1) or initiated but not completed (table 2)…"?FINE] since the end date of our literature search (April 2014) (the reporting year of our previous review). **[A: the meaning of "the reporting year" is unclear. Could this be omitted, or clarified, eg "(the end date of the literature search in our previous review)"?DONE –unless you feel too clunky]** We separate these trials into three key mechanistic approaches—immunomodulation, neuroprotection, and remyelination and repair—and within these sections describe phase 3 followed by phase 2b studies.

Immunomodulatory approaches [Prod: H3]

Most of the phase 3 trials completed **[A: completed?]** since 2014 tested **[A: can "powerful" be clarified? Powerful in what way? OK removed]** immunomodulatory treatments. Two trials **[A: or "Two approaches", to better match the text outside the brackets? Or should we reword so the trial names are outside of the brackets?YES AGREE lets do this]** have had practice-changing positive results: anti-CD20 treatment (with ocrelizumab, in ORATORIO) in primary progressive multiple sclerosis,[5] and sphingosine-1-receptor modulation (with siponimod, in EXPAND) in secondary progressive multiple sclerosis; table 1).[6]

ORATORIO and EXPAND showed that fewer people reached Expanded Disability Status Scale (EDSS) disability progression that was confirmed after 3 months (relative reduction 20–25%, absolute reduction 6%) with the new therapies compared with placebo. **[A: correct clarifications?YES]** These studies were well powered time-to-event trials, including distinct primary progressive and secondary progressive multiple sclerosis populations, testing interventions with known immunomodulatory mechanisms of action. The high degree of baseline inflammatory disease activity compared with other progressive multiple sclerosis trials (22–27% of participants given gadolinium had enhancing lesions at baseline) is likely to have increased the proportion of participants who responded to therapy. **[A: please clarify what you mean by bolstered in this context. Is likely to have increased the proportion of participants who responded to therapy? AGREED] [A: post-hoc or prespecified?POST HOC]** Subgroup analyses also suggest that treatment effects were greatest in participants who were younger and had greater inflammatory activity. This observation limits the external validity of these results to unselected populations of people with progressive multiple sclerosis, which is reflected in regional approval of these therapies. **[A: "in the use of these therapies" or "in the approval of these therapies"?OK]** For example, the European Medicines Agency restricts the use of siponimod and ocrelizumab to people who have progressive multiple sclerosis with evidence of inflammatory disease activity.[7,8]

An important lesson from ORATORIO and EXPAND is **[A: changes suggested as the rest of the sentence seems to describe only a single lesson. If there are multiple lessons, can they be more clearly distinguished? "could be amenable to immunomodulatory interventions in cohorts with relatively active disease, if outcomes are sufficiently responsive, and if follow-up is sufficiently long"?AGREED]** that progressive multiple sclerosis could be ameliorable to immunomodulatory interventions in cohorts with relatively active disease and using responsive outcomes, if there is sufficiently long follow-up. This is consistent with **AGREED**results from trials of other disease-modifying therapies, including fingolimod in people with primary progressive multiple sclerosis (INFORMS)[9] and natalizumab in people

with secondary progressive multiple sclerosis (ASCEND).[10] In INFORMS,[11] fingolimod did not meet its primary outcome at 3 years, with a relatively low proportion of participants who had **[A: or "with the low proportion of participants who had?OK]** baseline gadolinium activity (13%). In ASCEND, despite 24% of participants having gadolinium-enhancing lesions at baseline, natalizumab did not meet its primary outcome at 2 years. However, secondary outcomes—including upper limb function and composite disability measures in the open-label extension—suggested potential benefits with treatment. Although these secondary results should not be overinterpreted given the negative primary outcome, upper limb disability might be more responsive than lower limb disability **[A: than lower limb disability? If not, than what? YES]** to the immunomodulatory effects of natalizumab within a 2-year trial, and neurodegenerative processes precipitated by previous inflammation might be the predominant mechanism by which lower limb disability continued to worsen.[12]

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The PROMESS trial[13] of cyclophosphamide and methylprednisolone recruited only 45% of the planned sample size, and funding for a trial of pulsed adrenocorticotropic hormone was terminated **[A: can we say why?WE DON'T KNOW]** (NCT01950234). Cyclophosphamide and methylprednisolone are generally not used in standard practice for long-term treatment of progressive multiple sclerosis.[4]

Masitinib (a tyrosine-kinase inhibitor) **[A: please clarify how this relates to the paragraph above. It currently looks like masitinib is also an older compound, is that right? If not, wWhy does this follow the two older ones?REMOVED OLDER ETC ABOVE]** showed a positive result at 4·5 mg/kg per day[14] **[A: can we omit "in a separate trial cohort? Explaining how this cohort differs from the previous one might need more detail than we have room for helpful here AGREE]** The primary outcome, the overall mean change in EDSS, was atypical for modern trials, which commonly use time-to-event progression metrics. A second, much larger (N=800 *vs* 300) phase 3 trial is ongoing using standard time-to-EDSS confirmed disability progression outcomes (MAXIMS)). **[A: add "MAXIMS"?PLEASE]** Trials of two Bruton tyrosine-kinase inhibitors, tolebrutinib (PERSEUS) and HERCULES) **[A: HERCULES? Can a name be added for other trials here? OK]** and fenebrutinib FENtrepid), are projected to enrol around 1000 participants each. **[A: still correct? If they are still enrolling, results in 2024 seem unlikely AGREED -REMOVED]** These small molecules have the potential to cross the blood–brain barrier and modulate CNS-resident innate macrophages, microglia, and B-cell lineages, which are thought to be key drivers of neuroinflammation.[15] The blood–brain barrier penetrance of each individual agent differs, however, with tolebrutinib potentially achieving higher concentrations than fenebrutinib.[16] The safety of this class remains to be defined, particularly regarding hepatotoxicity.[17]

In a phase 2b trial (table 2),[18] vidofludimus calcium, a small-molecule selective second-generation dihydroorotate dehydrogenase oral immunomodulator, reduced the cumulative number of active lesions in participants with relapsing-remitting multiple sclerosis); the drug is now being tested in a larger phase 2 trial in progressive multiple sclerosis (NCT05054140). Few of the other potential therapies tested in phase 2b trials were immunomodulatory compounds (table 1), with no benefit **[A: "no benefit"?OK]** seen for Tcelna (NCT01684761), an autologous cell-based immunotherapy that aims to reduce the number and activity of **[A: numbers of? Activity of?BOTH]** myelin-reactive T cells, or laquinimod,[19] a quinoline-3-carboxamide derivative with immunomodulatory effects on microglia and astrocytes.

Dimethyl fumarate, which has immunomodulatory and neuroprotective mechanisms via promotion of the nuclear factor erythroid-derived 2 transcriptional pathway and inhibition of the nuclear factor-κB signalling pathway, has been assessed in two separate phase 2b trials: it did not show an effect on CSF neurofilament light chain levels (NfL) in a population with primary progressive multiple sclerosis,[20] nor was any benefit reported on a composite clinical outcome in a cohort with secondary progressive multiple sclerosis (NCT02430532). However, hydroxychloroquine (an antimalarial drug that inhibits microglial activation and reduces disease severity in experimental autoimmune encephalomyelitis) exhibited non-futility using a Simon two-stage approach, **[A: should we cite figure 1 here rather than at the end of the sentence? AGREE]** with 23% of participants experiencing progression on the timed 25-foot walk test (fewer than would be historically expected), justifying further trials to definitively assess efficacy (figure 1).[21]

Given the expanding evidence implicating Epstein–Barr virus in the pathogenesis of multiple sclerosis, a further novel therapeutic approach is ATA188 (NCT03283826; an allogenic Epstein–Barr virus-directed cytotoxic T-cell therapy).[22] However, ATA188 did not meet its primary outcome of sustained EDSS disability improvement; further details and secondary outcomes are awaited.[23]

Stem cell autografts, using various lymphoablative or myeloablative protocols, have been assessed for treating relapsing-remitting multiple sclerosis but their role in progressive multiple sclerosis (both active and non-active) is unclear.[28] The BEAT-MS trial is testing **[A: or "is testing"?OK]** myeloablative autologous haematopoietic stem-cell transplantation in participants with relapsing-remitting or active secondary progressive multiple sclerosis (**[A: defined by?] (defined by** clinical relapses or new MRI lesions), with projected final data collection in 2026 (NCT04047628). **[A: correct that there will be three years between the end of the study and reporting?YES THAT WHAT IT SAYS ON CLINICAL TRIALS: ITS ODD** .
Primary completion date is 2026 and study completion is 2029. 2026 is the last patient out from the primary outcome. That said this study may be delayed anyway…

] Intravenous mesenchymal stem cells showed no effect in the MESEMS trial,[29] in which about one-third of the participants had active progressive multiple sclerosis, with the remainder having relapsing-remitting multiple sclerosis. In a smaller trial in progressive multiple sclerosis, significantly fewer patients **[A: with progressive multiple sclerosis?YES]** receiving either intrathecal or intravenous mesenchymal stem cells showed a worsening in EDSS parameters compared with sham treatment.[30]

As patients become older, the balance of multiple sclerosis pathology shifts from focal active inflammation towards a phenotype dominated by neurodegeneration and CNS-compartmentalised inflammation. Patients might, therefore, not need to continue currently licensed disease-modifying therapies. However, when and how to stop therapies is unknown. In the DISCOMS trial, 259 patients (17% with progressive multiple sclerosis) who were aged 55 years or older and had been clinically and radiologically stable on an approved multiple sclerosis therapy were randomly allocated either to stop or to continue their therapy.[31] Over 18–24 months, 4·7% of those who continued had disease activity, compared with 12·2% of those who discontinued. Most of those with disease activity had one or two new brain MRI lesions; very few had a clinical relapse. With an absolute difference of 7·5%, the investigators were unable to reject the null hypothesis that therapy discontinuation was non-inferior to

continuation. Patients and clinicians should discuss whether this difference merits continuation of immunomodulatory therapy.

Neuroprotection [Prod: H3]

By contrast with the progress made with immunomodulatory disease-modifying therapies, no phase 3 trials of neuroprotection have reported positive results. **[A: correct clarification?YES]** A small trial (n=154) of high-dose biotin showed a larger proportion of patients with confirmed disability improvement over 9 months (13% *vs* 0%) compared with placebo,[32] but this finding was not confirmed in a larger trial (n=642),[33] nor in another trial examining optic nerve function in a mixed cohort in which 22% of people has secondary progressive multiple sclerosis.[34] The MS-STAT2 trial (NCT03387670) is currently testing whether simvastatin can slow disability progression, after the phase 2b trial, MS-STAT **[A: MS-STAT?YES]** showed a 43% reduction in brain atrophy compared with placebo.[35] Ibudilast, which inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4, slowed whole-brain atrophy, cortical atrophy, and decline in magnetisation transfer ratio MRI in a phase 2b trial that included equal numbers of participants with **[A: do you mean "that included equal numbers of participants with"? YES]** primary progressive and secondary progressive multiple sclerosis.[36,37] The antioxidant lipoic acid[38] demonstrated a relative reduction of 68% in annualised progression of whole-brain atrophy **[A: please clarify "rate". Is this truly a value that is per a unit of time such as year we could add, or could "rate" be omitted?OK]** compared with placebo over 2 years and is now being tested further in the LAPMS (NCT03161028) and OCTOPUS (ISRCTN 14048364) trials.

MS-SMART was a multi-arm phase 2b trial evaluating amiloride (an acid-sensing ion channel **[A: channel?YES]** blocker, reducing calcium and sodium influx), fluoxetine (which stimulates glycogenolysis and improves mitochondrial metabolism), and riluzole (inhibition of glutamate release) **[A: please clarify. A glutamate receptor blocker? An inhibitor of glutamate release?OK]** compared with placebo.[25] None of the treatments slowed the progression of whole-brain atrophy **[A: or just "whole-brain atrophy"?OK]** over 96 weeks compared with placebo, despite some evidence of target engagement (riluzole was associated with a reduction in glutamate signal on magnetic resonance spectroscopy).[39] Likewise, no benefits were seen on the primary outcomes with either idebenone[40] (a synthetic quinone similar to coenzyme Q10, with proposed mitochondria protective effects) or epigallocatechin gallate (a polyphenolic green tea component with proposed anti-inflammatory and neuroprotective properties).[41]

New compounds being trialled at phase 2b include: N-acetyl cysteine (NCT05122559), an antioxidant that scavenges free radicals and restores neuronal glutathione;; **[A: should this be omitted from here as now introduced above? YES]** SAR443820 (NCT05630547), a small-molecule inhibitor of receptor-interacting protein kinase 1, involved in glial neuro-inflammatory responses; and nicotinamide riboside (NCT05740722), a nicotinamide adenine dinucleotide precursor with the potential to improve mitochondrial function.

Clinical trial methods for studying neuroprotection in progressive multiple sclerosis remain nascent. The current disappointing absence of a therapeutic effect for the majority of

compounds tested so far, **[A: please clarify which ones, as those mentioned most recently do not have results yet YES DONE]** which target a large variety of mechanisms, reflects, to an extent, the limits of our knowledge of human pathobiology. Targeting CNS-compartmentalised inflammation and peripherally driven inflammation concomitantly along with neuroprotective modalities, might be necessary. The regulatory approval pathway for such combination therapies is daunting, however, as regulators frequently require evidence that each component of a combination therapy makes a contribution to the overall therapeutic effect.[42,43]

Remyelination and repair **[Prod: H3]**

For individuals with multiple sclerosis who have accumulated **[A: please clarify "fixed", which suggests "irreversible", but that seems contrary to the efforts to promote repair, etc REMOVED FIXED]** neurological disability, therapies that remyelinate, promote repair, and restore function are sorely needed. Although no remyelinating or repair-promoting therapies have been approved, high-throughput models have facilitated screening for potential remyelinating compounds. Several research **[A: research?YES]** groups have studied the role of oligodendrocyte progenitor cells in remyelination with the use of high-throughput models allowing **[A: please clarify which methods. "high-throughput models allow"?YES]** screening of a large number of compounds for potential remyelinating effects,[44–46] which can then be taken into brain tissue assays, and then to in vivo remyelination animal assays.[47] For example, clemastine fumarate, a muscarinic receptor antagonist, was identified through a novel oligodendrocyte progenitor cell micropillar assay, subsequently validated in animal studies, and then studied in a phase 2b trial in participants with relapsing multiple sclerosis and **[A: relapsing-remitting multiple sclerosis and"?YES –THEY USED RELAPSING ALONE]** chronic optic neuropathy, where it was associated with improvement in visual evoked potential (VEP) P100 latency.[27]

In a phase 2b trial in people with relapsing-remitting multiple sclerosis (79%) or secondary progressive multiple sclerosis with relapses (21%), opicinumab, a monoclonal antibody directed at LINGO-1 (leucine-rich repeat and Ig-like domain-containing Nogo receptor interacting protein 1), did not show a consistent benefit on a multicomponent measure of disability improvement.[48] Likewise, in optic neuritis it did not show a benefit on VEP conduction latency in the intention-to-treat analysis.[49] Although opicinumab did not have a measurable remyelinating effect, this development programme provided important lessons in the clinical design of remyelinating trials. Key insights from this trial included: the use of an (**[A: can we add a few words here to clarify, eg "the benefit of studying an"?]** a specific**[A: or "specific"?]** pathway *vs* overall disability as outcome measures ;how to sequence studies in different MS populations; **[A: please clarify "sequence studies"]** and when to consider programme termination. The use of a neurologically eloquent **[A: or "specific"?]** pathway as an outcome measure for clinical trials (eg, optic nerve,[50] spinal cord, or ocular movements[51]) could mean that an effect of a remyelinating therapy is more discernible.

Domperidone, a D2 receptor antagonist that increases serum prolactin concentrations and improved remyelination in a mouse model of experimental demyelination, did not reduce the percentage of patients with worsening of disability and, therefore, will not be pursued further.[24] Elezanumab, a monoclonal antibody against repulsive guidance molecule A (a

potent inhibitor of axonal growth and regulator of neuronal cell death), improved remyelination and axonal regeneration in experimental autoimmune encephalomyelitis models. However, the RADIUS study did not show a benefit on the mean overall response score in participants with secondary progressive multiple sclerosis (NCT03737812).

Although not yet studied in people with progressive multiple sclerosis, retinoid receptor γ has been implicated in remyelination and has been investigated as a potential therapy in relapsing-remitting multiple sclerosis. In a phase 2b trial of bexarotene, a retinoid receptor agonist, in people with relapsing-remitting multiple sclerosis,[52] the primary outcome (mean lesion magnetisation transfer ratio) was negative, but secondary MRI endpoints, including cortical and deep grey matter lesional magnetisation transfer ratio and a per-protocol analysis of VEPs, suggested a potential remyelinating effect and supports the potential use of these imaging biomarkers for proof-of-concept remyelination trials in progressive multiple sclerosis.

Population to target [Prod: H2]

When designing a clinical trial, defining the target population according to the proposed therapeutic mechanism is helpful in identifying beneficial effects and determining generalisability of the findings. Factors to consider include inflammatory activity, multiple sclerosis subtype, race, ethnicity, and comorbidity.

Inflammatory activity [Prod: H3]

Focal inflammatory activity is an important factor in trials of therapies targeting peripherally driven inflammation. Among the phase 3 trials listed in table 1 in which the intervention showed a benefit, the proportion of participants with baseline gadolinium-enhancing lesions varied from 22% to 27%. In the EXPAND trial of siponimod,[6] 22% of participants undergoing gadolinium enhanced imaging at baseline had enhancing lesions **[A: do you mean "21% of participants had baseline gadolinium-enhancing lesion activity"? YES-IN FACT 22% (TABLE IN ORIGINAL TRIAL PAPER WRONG-ACTIVE ARM SHOULD ROUND TO 22%)-ADJUSTED ABOVE AS WELL-OUR TABLE CORRECT]** and the mean pretrial annualised relapse rate was 0·23, which is considered active for a secondary progressive population. The annualised relapse rate was reduced to 0·07 with siponimod compared with 0·16 for placebo. The ASCEND trial of natalizumab compared with placebo[10] (in which 24% of participants undergoing gadolinium enhanced imaging at baseline had enhancing lesions **[A: do you mean "in which 23.5% participants had "?]YES**) did not show a benefit in its primary outcome—a multicomponent **[A: do you mean "a composite"?-THEY USE MULTI-COMPONENT IN THE PAPER – I'D BE HAPPY WITH EITHER]** of EDSS, the timed 25-foot walk test, and the nine-hole peg test—although in-trial gadolinium-enhancing activity was suppressed and annualised relapse rate was reduced to **([A: "to" or "by"?OK]** 0·08 natalizumab *vs* 0·17 placebo). A fundamental decision for study sponsors, therefore, is whether the study population should be enriched for active or non-active progressive multiple sclerosis. Enrichment for activity increases the likelihood of progression of disability during the study and, based on existing trial data, seems to increase the probability of showing a treatment effect with peripherally targeting immunomodulatory therapies. However, it could also increase the proportion of

Commented [NR3]: Corrected this from 13%. The 13% figure comes from INFORMS, but this was a negative trial - and hence should not be included as this sentences relates to positive phase 3 only

patients with on-study disease activity that is unlikely to respond to purely neuroprotective or remyelinating therapies.[53] Disease activity (ongoing relapses, new MRI T2 lesions, or raised serum or CSF NfL), is a requirement for the DanNORMS trial (of rituximab *vs* ocrelizumab, both peripheral immunomodulators; NCT04688788), but HERCULES (tolebrutinib;) **[AE/A: remove NCT number as mentioned earlier?FINE]** and MAXIMS (masitinib;) target a non-relapsing population **[A: remove NCT number as mentioned earlier?FINE]**—both trials that aim to target CNS-compartmentalised inflammation.

Disease course subtype [Prod: H3]

The biological differences and disease trajectories between primary and secondary progressive multiple sclerosis are debated, but separation of these subtypes in clinical trials can be useful to reduce cohort heterogeneity, and most phase 3 trials have used this approach (tables 1 and 2).[54] Importantly, regulatory agencies have generally considered primary and secondary progressive multiple sclerosis to be separate and, if they are combined into one trial, expect the subgroups to be sufficiently powered for individual analysis.

Progression independent of relapse activity (PIRA) is an emerging concept that was originally described in the ocrelizumab phase 3 trials in relapsing-remitting multiple sclerosis.[55] Confirmed disability accumulation was defined as sustained worsening on the main clinical outcomes and was termed PIRA when it occurred in the absence of **[A: how recent?ADDED DETAIL]** relapse activity. A recent systematic review has identified heterogeneity in the criteria used to define PIRA, and suggests PIRA is defined as an events of confirmed disability worsening, excluding the period 30 days before, and up to 90 days after a relapse. Approximately 80% of all disability worsening in the trial was found to be PIRA. Conceptually, patients with PIRA could be said to have secondary progressive multiple sclerosis and, given that older age is associated with PIRA, whether it represents the onset of secondary progressive multiple sclerosis is not clear. Because PIRA occurs in relapsing-remitting multiple sclerosis, and brain volume loss occurs early in the disease process (silent progression),[56] neurodegeneration in relapsing phases of the disease might have early clinical consequences. **[A: changes suggested for brevity and clarity. Correct?FINE]** PIRA is not, however, synonymous with non-inflammatory neurodegeneration. A large proportion of patients with PIRA have inflammatory disease activity on MRI and, therefore, PIRA rates are reduced with licensed immunomodulatory disease-modifying therapies.[55,57] Future trials could consider accounting for neurodegenerative components of the disease with measures including PIRA and brain atrophy, perhaps even from diagnosis. **[A: or "from diagnosis", as the disease will probably not be detectable when the process starts?AGREE]**

Commented [NR4]: Sharrad, Dale, et al. "Defining progression independent of relapse activity (PIRA) in adult patients with relapsing multiple sclerosis: A systematic review." *Multiple Sclerosis and Related Disorders* 78 (2023): 104899.

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Race, ethnicity, and comorbidity [Prod: H3]

Increasingly, a lack of diversity of multiple sclerosis clinical trial populations is being acknowledged. **[A: or "recognised" or "acknowledged"? Other changes suggested for brevity OK]** Diversity has many aspects, such as age, sex, gender, race, ethnicity, comorbidity, and social determinants of health, and might contribute to heterogeneity of treatment effects. Although race and ethnicity should not be considered to designate genetically distinct groups, these and intersecting social determinants of health are associated with differences in clinical presentation, treatment responses, and outcomes.[58–60] For example, lower socioeconomic status is associated with more rapid disability progression, a higher burden of comorbidity, and increased mortality.[61,62] **[A: do we need "rate" here?OK]** A systematic

review of phase 3 clinical trials of disease-modifying therapies for multiple sclerosis **[A: for multiple sclerosis?OK]** examined how representative the study populations were with respect to race and ethnicity: of ten trials that enrolled people with progressive multiple sclerosis, only one reported the racial or ethnic characteristics of participants, of whom 90% identified as White.[63]

The prevalence of comorbidity is high in people with multiple sclerosis, rises with age, and is associated with disability progression.[64] For example, among 251 people with multiple sclerosis with an average EDSS score of 3·5, a 1-point increase in the Framingham cardiovascular risk score was associated with a nearly 20% increased rate of reaching an EDSS score of 6 over an average follow-up of 4·6 years.[65] These findings regarding comorbidity have several important implications for trial design. First, because comorbidities might influence expected relapse rates, disability progression, and imaging outcomes,[65–69] they could also influence sample size calculations. Second, individuals with comorbidities are likely to be treated for comorbidities that might independently influence the trial outcomes, interact to reduce or augment the effects of the trial intervention, or influence safety. For example, simvastatin is used to treat cardiovascular comorbidity and might also affect multiple sclerosis; it is now being tested in the MS-STAT2 trial. Third, treatment of comorbidities could be a potentially useful intervention for reducing disease progression in people with progressive multiple sclerosis. Finally, enrolment of participants who do not reflect the diversity of typical clinical populations reduces the generalisability of trial results to clinical practice.

Outcomes [Prod: H2]

The heterogeneity of progressive multiple sclerosis—clinically, pathologically and radiologically—creates a challenge for designing suitable outcomes.[2,53] Ideally, outcomes should be reliable (producing accurate and reproducible data), valid (measuring what they are meant to measure), and responsive (capable of detecting a change that results from an intervention).[70] linician-reported and patient-reported outcomes (primary and secondary) **[A: please clarify to what this refersOK]** are typically used in phase 3 trials as primary and secondary outcomes;, and intermediate biomarker outcomes are often employed in phase 2 studies.

Clinical and patient-reported outcomes [Prod: H3]

Clinician-assessed, performance-based, and patient-reported outcome measures used in progressive multiple sclerosis trials have been reviewed previously.[70] In table 3 we give brief details, and examples of their use in the trials from tables 1 and 2.

Despite its imperfections, the dominant clinician-assessed primary outcome in phase 3 trials remains the EDSS. Typically, it is used in a time-to-event manner, with confirmation at least 3 months or 6 months after the initial progression. Previously, licensing authorities have not recommend other outcome measures for the assessment of disability progression.[71] This position is exemplified by the Multiple Sclerosis Functional Composite, an unweighted Z-score combination of the nine-hole peg test, a timed 25-foot walk, and the Paced Auditory Serial Addition Test: a beneficial effect of interferon beta compared with placebo in participants with secondary progressive multiple sclerosis was previously shown using the a primary

outcome of this composite, but this finding was not accepted as sufficient for licensing purposes owing to uncertainty as to how this outcome related to clinically meaningful benefits for patients.[72] Moving forward, the validated definitions of clinically meaningful change on each outcome (table 3) allow for multicomponent assessments (such as EDSS-plus) to be used in time-to-event analyses. Such approaches should increase sensitivity to detect disability progression, in addition to maintaining a focus on clinically meaningful change;[71] an updated opinion from licensing authorities on such outcomes would be welcome. **[A: do you mean that one is already expected, in which case is there a reference and can we say which authorities and roughly when, or are you calling for an update, in which case can we say "we would welcome an updated opinion…", "an updated opinion on…would be welcome" or "an updated opinion on…is needed"?DONE]**

Patient-reported outcomes (PROs) collect data directly from patients without clinician interpretation. A systematic review[73] identified 405 PROs that have been used in multiple sclerosis research, of which 82 were specifically developed for multiple sclerosis. Efforts to address the lack of consensus on the use of PROs and their limitations are being coordinated by the Global Patient Reported Outcomes in Multiple Sclerosis initiative.[74] PROs are used as secondary outcomes and are often consistent with the primary result, although there can be exceptions, such as the Multiple Sclerosis Walking Scale 12 in EXPAND[6] and the Multiple Sclerosis Quality of Life 54 in the phase 3 trial of **[A: the phase 2 trial of?IN FACT PHASE 3 - IT WAS THE FIRST MASTINIB TRIAL]** masitinib.[14] A core set of PROs for use in all clinical trials would be very useful. Ongoing work is establishing the interdependence of the functional domains assessed by PROs, validating remote collection of PROs through electronic health care, and characterising clinically meaningful changes.[75] Following the disruption to clinical trial activity during the COVID-19 pandemic, the potential use of such remotely collected data seems high,[76] but at present data on the validity, reliability, and responsiveness of such remote outcomes to treatment is scarce.

Biomarkers **[Prod: H3]**

Biomarkers are often employed as treatment response indicators, particularly in phase 2 trials. Given the wide variety of disease processes that can be targeted in progressive multiple sclerosis trials, biomarkers should reflect the underlying biology of the mechanism of action being interrogated, although common end-stage processes can also be assessed; **[A: does this "targeted" mean "assessed"?YES]** biomarkers relevant for progressive multiple sclerosis include imaging, visual, and biofluid markers.

Whole-brain atrophy has been used extensively in multicentre trials because it is straightforward to derive, has well curated normative data, and reflects the overall**[A: or "overall"?YES]** disease process. Importantly, the effect of an intervention upon brain atrophy is also generally associated with the effect upon future physical disability (figure 2).[78]

[A: refs 79–81 not cited in text. Should they be cited in the fig 2 legend? YES THANK YOU – 79-81 SHOULD ALL BE INCLUDED AS REFERENCES IN FIGURE 2 LEGEND] Disadvantages of whole brain atrophy **[A: of whole brain atrophy?YES]** include within-individual and interscanner variability, poor pathological specificity, slow change over time, and little meaning at the individual-patient level.[82] Additionally, brain atrophy occurs relatively late, after significant

accumulation of tissue injury, and probably results from several mechanisms. Tissue loss also does not occur linearly in all **[A: brain?YES] brain** regions, and atrophy can vary based on age.[83,84] Ultimately, the usefulness of brain atrophy in progressive multiple sclerosis trials could be shown if positive results from phase 2b trials predict phase 3 success. An important test of this hypothesis **[A: please clarify. An important test of this hypothesis?YES]** will be the MS-STAT programme, which showed a benefit on simvastatin in reducing brain atrophy in the phase 2 trial [35] **[A: please clarify successful. Which showed a benefit of simvastatin using brain atrophy in the phase 2 trial"?YES]** and the ongoing phase 3 study, MS-STAT2 **[A: omit NCT number as mentioned earlier? Say MS-STAT2 instead?YES]** is using clinical progression is the primary outcome. As a caution, ASCEND[10] did not meet its primary outcome of slowing multicomponent clinical disability progression, although the treatment slowed progression of brain atrophy (figure 2).

Regional brain volumes, particularly those of grey matter structures, have also been proposed as clinical trial outcomes.[85] Cortical atrophy is a natural choice for trials examining neuroprotective effects. In the phase 2b trial of ibudilast, cortical thickness was among the measures that showed a significant effect and was not fully correlated with brain atrophy, which suggests it measures partly separate biological processes.[36] Thalamic atrophy also shows changes early in the disease course for both relapsing and progressive multiple sclerosis[86] **[A: early in the course of multiple sclerosis or the course of progressive multiple sclerosis?DONE]** and is associated with cognitive and physical disability;[87] it has been used as a secondary and exploratory outcome in several relapsing and progressive multiple sclerosis trials.[88,89] However, smaller brain structures, such as the thalamus, show greater measurement variability and might require larger sample sizes than are needed to assess effects on whole-brain atrophy.[85]

Spinal cord volume is another candidate outcome, although low signal-to-noise ratio, physiological movement, and an absence of standardised acquisition sequences present technical difficulties. Advances in spinal cord segmentation using brain images that contain upper cervical cord coverage[90] include methods that can correct for differences in spinal cord volume related to overall body and brain size..[91] **[A: can this sentence be simplified? The meaning might not be obvious to non-specialist readers. Normalise what? What sort of anatomical structures? How is specifically the upper cervical spinal cord relevant? DONE]** Spinal cord cross-sectional atrophy predicts long-term disability, is greater in progressive, than relapsing-remitting **[A: than relapsing-remitting?YES]** multiple sclerosis,[92] and is more predictive of disability than brain atrophy.[93] However, focal lesion development in the spinal cord might be a driver of disability, and segmenting lesional tissue in the spinal cord is difficult.[94] Registration-based longitudinal methods to characterise spinal cord atrophy hold promise as phase 2 clinical trial outcome measures.[95]

Several advanced imaging techniques have been developed to quantify CNS compartmentalised inflammation and myelination, each having advantages and disadvantages (table 4). Further validation and standardisation are required for application in multicentre trials, although the increasing use of these techniques as secondary outcomes should facilitate the appropriate matching of an outcome measure to the proposed mechanism of action of an intervention. Examples include the use of slowly expanding lesions or paramagnetic rim lesions as outcomes in trials of interventions targeting microglial

activation (eg, NCT05630547) and the use of magnetisation transfer ratio as an outcome for remyelinating interventions.[27] In addition to MRI, PET ligands with sensitivity to myelin or microglia have been proposed as potential trial outcomes for remyelination and CNS-compartmentalised inflammation, but the insufficient multicentre validation and feasibility issues (tracer availability, expense, low resolution, and expertise required) are currently barriers to widespread use.[96]

Both functional (VEP) and structural (optical coherence tomography) visual biomarkers have been used in multiple sclerosis trials. Multifocal VEPs can be measured by selectively stimulating different regions of the retina, thereby assessing a larger area of the optic nerve, than standard VEP **[A: than with what method? THIS]** and potentially increasing sensitivity to small areas of demyelination.[97] Visual measures appear most promising in phase 2b remyelination trials, where they have been used as primary outcomes, but importantly also as inclusion criteria. The ReBUILD trial (figure 1) recruited patients without a recent history of optic neuritis but with baseline full-field VEP latency of more than 125 ms and retinal nerve fibre layer thickness greater than 70 µm.[27] The rationale was to select participants with stable chronic visual pathway demyelination, but with sufficient remaining axons upon which remyelination might occur. In contrast to VEPs, optical coherence tomography biomarkers might be more applicable as measures of neuroprotection, as retinal nerve fibre layer or ganglion cell layer thickness represent axonal and neuronal densities.[98] Although optical coherence tomography has practical advantages over MRI in terms of cost and speed of data acquisition, larger sample sizes are likely to be needed.[99–101]

In progressive multiple sclerosis, NfL levels, whether measured in serum, plasma, or CSF, are strongly associated with recent neuroinflammatory-driven neuroaxonal injury.[102] NfL is therefore a responsive biomarker of immunomodulatory treatments that targets focal inflammation, as shown by positive treatment effects compared with placebo when used with ocrelizumab, siponimod, fingolimod, and natalizumab in progressive multiple sclerosis trials.[102] By contrast, the performance of NfL as a biomarker of neuroprotection with candidate non-immunomodulatory compounds has been disappointing. Acknowledging the low **[A: "absence of" or "low"?OK LOW]** pathological specificity of brain atrophy and that confirmation of efficacy at phase 3 for both simvastatin and ibudilast is still awaited, post-hoc analyses of the MS-STAT (simvastatin)[103] and SPRINT-MS (ibudilast)[104] phase 2b trials showed that significant reductions in whole-brain atrophy and other imaging measures were not accompanied by a beneficial effect on NfL levels. Conversely, the ASCEND (natalizumab) and INFORMS (fingolimod) trials showed a benefit of treatment on NfL but not clinical outcomes.[102] The central link between neuroinflammation and NfL is also supported by further analyses from ASCEND: once active inflammation is treated with natalizumab, NfL no longer predicts future disability progression.[105] Hence, novel candidate fluid biomarkers of non-inflammatory neurodegeneration are urgently needed. Serum glial fibrillary acidic protein has a stronger relationship with future PIRA and is less dependent on acute neuroinflammation compared with NfL.[106] Accordingly, glial fibrillary acidic protein warrants continued investigation in progressive multiple sclerosis. Other approaches include proteomic and microarray techniques, which appear promising for the simultaneous assessment of multiple biomarkers that might quantify diverse but overlapping processes.[107,108]

Trial design and direction setting [Prod: H2]

[A: suggested combination of sections we try to avoid single-paragraph sections at this levelYES HAPPY WITH THAT] All published phase 3 trials used a standard placebo control versus active arm design (either 1:1 or 2:1; table 1). Most also used time to confirmed disability progression as the primary outcome, and this remains the case in ongoing trials (table 2). Trial efficiency needs to be improved to reduce the time and costs required. Figure 1 illustrates some examples of alternative trial designs for multiple sclerosis.[109]

Public and patient involvement increasingly occupies a central role in setting priorities and directions for progressive multiple sclerosis research. Such involvement in research is an active partnership—ideally throughout the lifespan of a research project—between researchers and patients, their families and caregivers, and the lay public to plan, manage, design, and conduct research, and it is a vital but often missed component of the research process. Active public and patient involvement in research design and delivery significantly increases the quality of research studies, by **[A: add "by"? If not, quality assessed how? YES]** improving enrolment and retention[110] and making the findings more likely to be relevant and implemented.[111] For example, the OCTOPUS trial was co-designed by people affected by progressive multiple sclerosis.[112] Public and patient involvement workshops were held across the UK, which highlighted the importance of messaging about the purpose and outcomes of the trial, and led to the option for rerandomisation for patients in a treatment group that was stopped. Co-design influenced the trial design, treatment selection, and recruitment materials, thereby developing a trial that works for people with multiple sclerosis and researchers.[112]

Increasing academic collaboration under the stewardship of multiple organisations has further focused the field on advances for people with progressive multiple sclerosis. Such organisations include ECTRIMS, MAGNIMS, ACTRIMS, NAIMS, CMSC, and IPSMA. **[Prod: margin links:**

For more on ECTRIMS see https://ectrims.eu

For more on MAGNIMS see https://www.magnims.eu

For more on ACTRIMS see https://forum.actrims.org

For more on NAIMS see https://www.naimscooperative.org

For more on CMSC see https://www.mscare.org/default.aspx

For more on IPMSA see https://www.progressivemsalliance.org] Outputs include building consensus on topics such as the use of imaging in diagnosis and monitoring,[113] outcome measures for interventions targeting remyelination[96] and CNS-compartmentalised inflammation,[114] a revised mechanism-driven framework for conceptualising multiple sclerosis progression and approaches to treatment,[2] and a recent publication on trial design.[109]

Conclusions and future directions [Prod: H2]

A step change has taken place in the treatment of progressive multiple sclerosis since we published our previous review,[4] with the approval of immunomodulatory treatments for clinical use, particularly for people with active inflammatory disease. Reasons for recent phase 3 success include a tighter matching of trial cohort characteristics such as inflammatory disease activity to drug mechanism, well powered time-to-event designs, and active regulatory dialogue to ensure that planned outcomes are clinically relevant. **[A: and dialogue with drug regulators? How as this dialogue led to phase 3 trial success, as that isn't apparent above?]** However, the therapeutic gains are modest. Further success could be achieved as novel immunomodulatory mechanisms—particularly those targeting elements within the CNS, such as microglia **[A: what sort of elements?]** within the CNS—complete trials over the next few years. **[A: in 2024 and 2025?ALTERED]**

The situation with neuroprotection, remyelination, and repair appears much more challenging, than immunomodulatory therapies **[A: than that for immunomodulatory therapies?AGREE]** exacerbated by uncertainties regarding in the vivo biology of progressive multiple sclerosis, currently resulting in no approved treatments. However, several promising interventions are working their way through the later stages of development, with interim outcomes **[A: increasingly robust in what way? interim outcomes that are increasingly being associated with clinical benefits?MORE THAT SIGNAL BEING SEEN ON SAY ATROPHY OR VEP]** showing positive signals. **[A: "showing evidence of benefits" or "showing preliminary evidence of benefits"?NOT THAT]** There is still a need to increase trial efficiency and to carefully consider the outcome measures deployed. Meaningful involvement of people affected by progressive multiple sclerosis is vital to maintain orientation to the issues that are most important to them. Finally, global collaboration will reduce redundancy, encourage the distribution of ideas, and ultimately increase the chance of further success.

Contributors

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Declaration of interests

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Commented [J6]: ACADEMIC Trial

Commented [J7]: Commercial and updated

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Figure legends

Figure 1: **Alternatives to the standard parallel group design in multiple sclerosis clinical trials**

(A) Early candidate treatments might be efficiently screened in low-cost, single-arm Simon two-stage futility studies, compared with historical controls.[21,22] Treatments appearing non-futile then enter further controlled studies to assess efficacy. (B) This is a multi-arm phase 3 trial with an interim analysis, denoted as multi-arm multi-stage (MAMS) **[A: can "phase 2b" be added to the figure? Please clarify for readers. Currently you show only stage 1 and stage 2, and it is not clear how the stages relate to phases or how phase 2b relates to the figure]** Multi-arm trials improve efficiency, **[A: compared with single-arm trials (suggested by the contrast with "multi-arm, but not by the later mention of placebo arms. Compared with two-arm trials?]** requiring fewer participants due to the shared placebo-controlled groups (eg, MS-SMART[23]), **[A: multi-arm trials are not obviously shown in A. Should this part of the legend be for B? If not, how does this multi-arm trial differ from the one in B?]and here multi-arm multi-stage** allowing interventions with positive interim results to continue recruitment and follow-up until a definitive final analysis (phase 3) is reached. **[A: correct that the standard of care and treatment B are shown with arrows continuing beyond the final analysis? Should these be blunt-ended lines, or arrows ending at a vertical line that indicates final analysis?] [A: the text mentions a treatment C but one is not shown. Should that be added, and if so can you please clarify where its bar should begin and end?] [A: please clarify "stage 2 selection" of what? Selection of interventions to proceed to stage 2?]** Conversely, ineffective interventions can be halted, allowing participants to be randomly allocated again and new interventions introduced (eg, OCTOPUS). (C) Multiple interventions can also be assessed in factorial designs (eg, CogEx[24]). (D) For interventions predicted to have short-term effects on an intermediate outcome and that can be washed out, crossover trials can enhance trial power (eg, ReBUILD[25]). T25FW=timed 25-foot walk. **[A: you have a randomisation step in D. Should randomisation be added to B, and if so where and how?]**

Commented [VL8]: Should refer to part B.
Really MAMS trials are multi-arm phase 3 with an interim analysis (there are can be more than 1). They are not seamless phase 2/3. I have rewritten the text

Commented [VL9]: Arrows for standard of care can extend beyond final analysis line. Arrow for treatment B should end with final analysis with blunt ended line.

If space allows, a treatment C could begin at the interim analysis red dashed vertical line with arrow continuing beyond the final analysis line similar to standard of care arrow.

Commented [VL10]: Corrected as suggested

Commented [VL11]: Technically yes, randomisation occurs before assigning treatment arm.

Figure 2: **Comparison of treatment effects upon whole-brain atrophy with treatment effects on disability progression reported in phase 2 and phase 3 trials in progressive multiple sclerosis**

[A: should there be units for disability progression?] [A: correct to imply that lamotrigine, natalizumab, and lipoic acid seem to increase disability progression?NO –THESE ARE THE POINT ESTIMATES; THE SIZE OF THE CIRCLE IS PROPORTIONAL TO THE TRIAL SIZE AND NOT CI AS NOW MADE EXPLICIT [A: the y axis spacing seems to be different above and below 1. Is there a justification for this that could be explained for readers?] Y-axis: treatment effect on disability progression ((hazard ratio for time to confirmed 6 months EDSS disability progression. X-axis: mean difference

in yearly percentage change in whole brain volume from baseline. The treatment effects of interventions on whole-brain atrophy tend to (though do not always) reflect the treatment effect on disability progression.[5,6,9,10,33,34,36,76–79] The size of each circle is proportional to the trial size (confidence intervals are not given) - .Reproduced from Li et al.[77]

Search strategy and selection criteria [Prod: unlinked panel]

Our previous review had a search end date of April 5, 2014. Therefore, we searched for articles in MEDLINE All via OVID, Embase via OVID, and Cochrane Central Register of Controlled Trials (CENTRAL) for articles added to the databases between April 6, 2014, and Aug 20, 2023. **[A: can this be updated? YES YOU HAVE]** For trials published or presented **[A: in what way, eg at scientific conferences? Or can we delete this to avoid confusion, as a trial presented at a conference before April 2014 but published afterwards would presumably still be included PLEASE DELETE]** before April **[A: 6?]** 2014, we direct readers to our previous review. We also did a supplementary search for additional ongoing studies on ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) on Aug 20, 2023. **[A: any update? YOU HAVE]** The search strategy for MEDLINE and Embase combined indexed and free-text terms for progressive multiple sclerosis (eg, "multiple sclerosis", "chronic progressive", SPMS or SP-MS or PPMS or PP-MS) with study design filters (eg, "randomized controlled trial", "controlled clinical trial" [single, double, triple randomisation; blinded or masked]). For CENTRAL, ClinicalTrials.gov, and ICTRP, progressive multiple sclerosis terms were adapted from the MEDLINE search; no study design filter was required for these trial-focused databases. The searches excluded animal studies but no language restrictions were applied.