Appendix 1_Review protocols

Question 1	**In patients with CIS (regardless of whether they fulfil criteria for MS), what is the benefit of starting treatment with a disease-modifying drug (DMD) compared to no treatment?**
Population	Patients with a single clinical attack[a], regardless of number of MRI lesions
Interventions	• interferon beta/peg-interferon • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • natalizumab • alemtuzumab • daclizumab • ocrelizumab • mitoxantrone •
Comparators	Placebo or active comparator
Outcomes	<u>Efficacy outcomes</u> • Relapse (time to second relapse, % of participants with second relapse) • Disability worsening (measured on the EDSS) • Conversion to clinically definite MS <u>MRI outcomes</u> • New T2 lesions (presence of new T2/volume) • GAD lesions (presence of gad/volume) • Brain atrophy <u>Tolerability and safety outcomes</u> • Discontinuation (any reason/due to side effects) • Adverse events (specific events outlined for each drug – see appendix 7) • Mortality <u>Other outcomes</u> • Quality of life (patient reported) • Cognitive impairment
Exclusion	Pediatric population, studies evaluating combination of drugs, unlicensed doses, studies with <10 participants per arm, non-English language
Study design	RCTs with at least 1 year follow-up (48 weeks acceptable) Long term extensions on included RCTs

a. Clinical definition with slight variations between studies. Generally, first isolated, well-defined unifocal or multifocal neurologic event consistent with demyelination and involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brain stem or cerebellum (brain-stem or cerebellar syndrome) that was confirmed on ophthalmologic or neurologic examination.

Question 2	**In patients with relapsing-remitting MS and secondary progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?**
Population	Patients with a relapsing-remitting MS[a] only, patients with secondary progressive MS[b] only, studies with mixed population (both RR and SP)

Interventions	• interferon beta/peg-interferon • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • natalizumab • alemtuzumab • daclizumab • ocrelizumab • cladribine • mitoxantrone •
Comparators	Placebo or any active comparator
Outcomes	<u>Efficacy outcomes</u> • Relapse (% patients free of relapses, annualized relapse rate) • Disability worsening (measured on the EDSS) • Conversion to SPMS (in RR patients) <u>MRI outcomes</u> • New T2 lesions (presence of new T2/volume) • GAD lesions (presence of gad/volume) • Brain atrophy <u>Tolerability outcomes</u> • Discontinuation (any reason/due to side effects) • Adverse events (specific events outlined for each drug – see appendix 7) • Mortality <u>Other outcomes</u> • Quality of life (patient reported) • Cognitive impairment
Exclusion	Pediatric population, studies evaluating combination of drugs, unlicensed doses, studies with <10 participants per arm, non-English language
Study design	RCTs with at least 1 year follow-up (48 weeks acceptable) Long term extensions on included RCTs

a. clinically definite or laboratory-supported definite relapsing-remitting MS according to Poser criteria in the oldest trials and according to the revised McDonald criteria (2001 or 2005) in the most recent trials. Any additional criteria of number of relapses in the years prior to inclusion is valid.
b. clinical definition with variations between studies but all reflecting a progressive deterioration of disability with an increase in the EDSS, with or without superimposed exacerbations, following an initial RR course.

Question 3	**In patients with primary progressive MS what is the benefit of treating with *a DMD* compared to no treatment**
Population	Patients with primary progressive MS*
Intervention	• interferon beta/peg-interferon • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • natalizumab • alemtuzumab

	• daclizumab • ocrelizumab • mitoxantrone
Comparator	Placebo or any active comparator
Outcomes	Efficacy outcomes • Disability worsening (measured on the EDSS) Tolerability outcomes • Discontinuation (any reason/due to side effects) • Adverse events (specific events outlined for each drug – see appendix 7) • Mortality Other outcomes • Quality of life (patient reported) • Cognitive impairment
Exclusion	Pediatric population, combination of drugs, unlicensed doses, studies with <10 participants per arm, non-English language
Review strategy	• RCTs with at least 1 year follow-up (48 weeks acceptable). • Long term extensions on included RCTs

Question 4	**In patients with relapsing MS treated with DMDs, does the presence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 months/12 months) predict an increased risk of future disability?**
Population	Patients treated with DMDs (regardless type of drug and time on treatment)
Predictor	Presence of *early* (at 6/12 months) disease activity (relapses and/or disability accumulation and/or MRI activity[a])
Outcomes	Sensibility, specificity Long-term undesirable outcomes: • disability accumulation • secondary progressive MS
Exclusion	Studies assessing early disease activity at >12 months after treatment start, studies included paediatric population, non-English language
Review strategy	• Systematic reviews • RCTs • Observational studies

a. defined as the presence of new lesions or gadolinium enhancing lesions

Question 5	**In MS patients treated with DMDs, should a follow-up MRI be performed within a prespecified time scheme to monitor treatment response?**
Population	Patients treated with DMDs (regardless type of drug and time on treatment)

Intervention	MRI performed at fixed intervals to monitor treatment response
Comparator	MRI performed without fixed intervals to monitor treatment response
Outcomes	Monitoring MRI *early* treatment response (presence of new lesions and gad lesions)
Exclusion	Pediatric population/ MRI performed to monitor safety
Review strategy	Any study design would be valid for this question.

Question 6	**In patients with relapsing MS treated with interferon or glatiramer acetate and with evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?**
Population	Patients treated with first line DMDs[a] (regardless type of drug and time on treatment) and evidence of disease activity[b]
Intervention	Change between fist-line DMDs
Comparator	Escalate to a highly efficacious DMD[c]
Outcomes	• Relapse (% of participants, annualised relapse rate) • Disability worsening (measured on the EDSS) • MRI activity (number of new T2 lesions/gad lesions) • Side effects
Study design	• Systematic reviews • RCTs • Observational studies (prospective and retrospective cohorts)
Exclusion	Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language

a. such as INF, GA, teriflunomide and dimethyl fumarate.
b. several definitions could be used between studies (EDA, MEDA, Rio score...), combining clinical (relapses and disability accumulation) and MRI parameters
c. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab.

Question 7	**In patients with relapsing MS who stop taking a highly efficacious drug, is there a risk of return and/or rebound of their disease activity (increased risk of relapses, disability progression and/or MRI activity)?**
Population	Patients with relapsing MS treated with highly efficacious DMDs[a] for at least 12 months
Intervention	Treatment stop (any intervention after stop is acceptable)
Comparator	No comparator required
Outcomes	Annualised relapse rate/% with relapse (prior to current second line drug and after drug discontinuation) MRI outcomes (prior to current second line drug and after drug discontinuation) *All outcomes post-discontinuation to be reported within 6 months of stopping drug*

Exclusion	Pediatric population , patients receiving second-line DMD for less than 12 months, studies reporting outcomes measured after 6 months from drug switch, studies with <10 participants per arm, non-English language
Review strategy	• Systematic reviews • Observational studies (before-and-after studies)

a. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab
b. we will not distinguish between return or rebound. We will adopt any study definition that involves increase in relapses and/or disability progression and/or MRI activity as compared to that while on treatment

Question 8	**In patients with relapsing MS who stop taking a highly efficacious drug, what is the benefit of further treatment?**
Population	Patients with relapsing MS treated with highly efficacious DMD[a] **for at least 12 months** who stop treatment for safety issues
Intervention	Other highly efficacious DMD[a]
Comparator	• First line DMD • Remain untreated
Outcomes	• Relapse (annualised relapse rate/% of participants with relapse) • Disability worsening (measured on the EDSS) • MRI activity (number of new T2 lesions/gad lesions) • Conversion to SPMS • Side effects
Review strategy	• Systematic reviews • RCTs • Observational studies
Exclusion	Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language

a. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab

Question 9	**In patients with relapsing MS treated with DMDs that remain stable over a long time period, what is the benefit of continuing treatment compared to stopping?**
Population	Patients with MS treated with any DMD who show clinical stability[a]
Intervention	Discontinue DMD
Comparator	Continue on current DMD
Outcomes	• Relapse (time to relapse, annualised relapse rate, % of participants with relapse) • Disability worsening (measured with the EDSS) (time to worsening, % of participants) • MRI activity (number of new T2/GAD lesions) • Conversion to SPMS
Exclusion	Pediatric population, case-control studies, participants with clinical stability for <3 years, studies with <10 participants per arm, non-English language

Study design	• Systematic reviews • RCTs • Observational studies (prospective or retrospective cohorts)

a. absence of relapses and disability accumulation and MRI activity (no new lesions, no gad lesions)

Question 10	**In women with MS treated with DMDs who wish to start a pregnancy or who have an unplanned pregnancy, what should be the therapeutic approach?**
Population	Women with MS treated with DMDs (any type of drug and time on treatment)
Intervention	Stop treatment before trying to become pregnant
Comparator	Stop treatment when aware of being pregnant Continue treatment during pregnancy
Outcomes	• Spontaneous abortion • Low birth weight • Infant congenital malformation • Neonatal death • Relapse (prior to pregnancy and in the post-partum period)
Exclusion	Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language
Review strategy	• Systematic reviews • Observational studies (prospective and retrospective cohorts)