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)

Appendix 2_ Search strategies

Review Questions 1-3

Databases: Central, Embase, Medline, PreMedline, PsycINFO
Date Range: inception to December 2015
Hits Deduped: 6217 (Central: 1808; Other: 4409) Undeduped: 9532 (Central: 2250; Other: 7282) *Notes: references excluded from Central's screen for reports of trials (n2940) imported into a separate EndNote Library; these are unlikely to need a sift.*

- Embase, Medline, PreMedline, PsycINFO - OVID

#	searches
1	exp *multiple sclerosis/ or *myelitis/
2	1 use emez
3	exp multiple sclerosis/ or myelitis, transverse/
4	3 use mesz, prem
5	exp multiple sclerosis/ or myelitis/
6	5 use psyh
7	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
8	or/2,4,6-7
9	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
10	interferon beta serine.sh. use emez
11	interferon-beta.sh. use mesz, prem or interferon type i.sh. use mesz, prem
12	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
13	or/10-12
14	beta1a interferon.sh. use emez or recombinant interferon.sh. use emez
15	interferon-beta.sh. use mesz, prem or interferon type i.sh. use mesz, prem

#	searches
16	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
17	or/14-16
18	peginterferon beta1a.sh. use emez
19	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
20	or/18-19
21	glatiramer.sh. use emez
22	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
23	or/21-22
24	teriflunomide.sh. use emez
25	(aubagio or teriflunomid*).ti,ab.
26	or/24-25
27	fumaric acid dimethyl ester.sh. use emez
28	fumarates.sh. use mesz, prem
29	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
30	or/27-29
31	fingolimod.sh. use emez
32	(fingolimod* or gilenia or gilenya).ti,ab.
33	or/31-32
34	natalizumab.sh. use emez
35	(antegren or natalizumab or tysabri).ti,ab.
36	or/34-35
37	alemtuzumab.sh. use emez
38	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
39	or/37-38
40	daclizumab.sh. use emez
41	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
42	or/40-41
43	ocrelizumab.sh. use emez
44	(monoclonal antibod* or ocrelizumab or rhumab 2h7).ti,ab.

#	searches
45	or/43-44
46	mitoxantrone.sh. use emez,mesz
47	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.
48	or/46-47
49	cyclophosphamide.sh. use emez,mesz
50	(alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo cell or cycloblastin* or cyclofos amide or cyclofosfamid* or cyclofosphamid* or cyclophar or cyclophosphamid* or cyclophosphan* or cyclostin or cycloxan or cyphos or cytophosphan* or cytoxan or endocyclo phosphate or endoxan* or endoxon asta or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).ti,ab.
51	or/49-50
52	azathioprine*.sh. use emez,mesz
53	(arathioprin or arathioprine or aza q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin* or azathiopurin* or azathropsin* or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin* or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or thioazeprin* or thioprin* or transimun* or zytrim).ti,ab.
54	or/52-53
55	((corticosteroid* or steroid*) adj2 puls*).ti,ab.
56	or/9,13,17,20,23,26,30,33,36,39,42,45,48,51,54-55
57	exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/
58	57 use emez
59	exp clinical trial/ or exp "clinical trials as topic"/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/
60	59 use mesz, prem
61	(clinical trials or placebo or random sampling).sh,id.
62	61 use psyh
63	(clinical adj2 trial*).ti,ab.
64	(crossover or cross over).ti,ab.
65	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.

#	searches
66	(placebo* or random*).ti,ab.
67	treatment outcome*.md. use psyh
68	animals/ not human*.mp. use emez
69	animal*/ not human*/ use mesz, prem
70	(animal not human).po. use psyh
71	(or/58,60,62-67) not (or/68-70)
72	8 and 56 and 71
73	(2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,yr. use emez
74	(2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dd,yr. use mesz, prem
75	72 and (73 or 74)
76	72
77	limit 76 to yr="1860 - 2010"
78	76 not 77
79	remove duplicates from 77
80	remove duplicates from 78
81	from 79 keep 3938-3995
82	from 80 keep 3212-3317
83	from 72 keep 9037-9458
84	or/75,81-83

- CENTRAL - Wiley

#	searches
1	MeSH descriptor: [Multiple Sclerosis] explode all trees
2	MeSH descriptor: [Myelitis, Transverse] this term only
3	(((disseminated or insular or multiple or multiplex) near/2 scleros*) or “chariot disease” or “encephalomyelitis disseminate” or “transverse myelitis”):ti,ab,kw. or ms:ti
4	#1 or #2 or #3
5	((disease near/2 modif* near/2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* near/1 (modulat* or suppress*))) near/2 (agent* or drug* or therap* or treat*))):ti,ab,kw.
6	MeSH descriptor: [Interferon-beta] this term only

#	searches
7	MeSH descriptor: [Interferon Type I] this term only
8	(beneseron or “beta 1b interferon” or “beta1b interferon” or “beta interferon” or betaferon or betaseron or extavia or fiblaferon or “fibroblast interferon” or “ifn b” or ifnb or “ifn beta” or ifnbeta or “interferon beta” or “interferon fibroblast” or “rifn beta 1b” or “rifn beta1b”):ti,ab,kw.
9	#6 or #7 or #8
10	MeSH descriptor: [Interferon-beta] this term only
11	MeSH descriptor: [Interferon Type I] this term only
12	(avonex or “beta 1a interferon” or “beta1a interferon” or cinnovex or “ifn a” or ifna or rebif or “rifn beta”):ti,ab,kw.
13	#10 or #11 or #12
14	(“beta 1a peginterferon” or “beta1a peginterferon” or “peginterferon beta 1a” or “peginterferon beta1a” or (pegylated near/2 “interferon beta 1a”) or (pegylated near/2 “interferon beta1a”) or plegridy or (peginf or “peg inf”)):ti,ab,kw.
15	(“cop 1” or copaxone or “copolymer 1” or “copolymer cop 1” or “copolymer I” or glatiramer or glatopa):ti,ab,kw.
16	(aubagio or teriflunomid*):ti,ab,kw.
17	MeSH descriptor: [Fumarates] this term only
18	(“dimethyl fumarate” or “dimetil fumarate” or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or “trans butenedioic acid dimethyl ester” or tecfidera):ti,ab,kw.
19	#17 or #18
20	(fingolimod* or gilenia or gilenya):ti,ab,kw.
21	(antegren or natalizumab or tysabri):ti,ab,kw.
22	(alemtuzumab or campath or “cd52 monoclonal antibody” or emtrada or lemtrada or mabcampath or “monoclonal antibody cd52”):ti,ab,kw.
23	(daclizumab or dacliximab or dacluzimab or zenapax):ti,ab,kw.
24	(“monoclonal antibod*” or ocrelizumab or “rhumab 2h7”):ti,ab,kw.
25	MeSH descriptor: [Mitoxantrone] this term only
26	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*):ti,ab,kw.
27	#25 or #26
28	MeSH descriptor: [Cyclophosphamide] this term only
29	(alkyroxan or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or “cyclo cell” or cycloblastin* or “cyclofos amide” or cyclofosfamid* or cyclofosphamid* or cyclophar or cyclophosphamid* or

#	searches
	cyclophosphan* or cyclostin or cycloxan or cyphos or cytophosphan* or cytoxan or endocyclo phosphate or endoxan* or "endoxon asta" or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid):ti,ab,kw.
30	#28 or #29
31	MeSH descriptor: [Azathioprine] this term only
32	(arathioprin or arathioprine or "aza q" or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin* or azathiopurin* or azathropsin* or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin* or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or thioazeprin* or thioprin* or transimun* or zytrim):ti,ab,kw.
33	#31 or #32
34	((corticosteroid* or steroid*) near/2 puls*):ti,ab,kw.
35	#5 or #9 or #13 or #14 or #15 or #16 or #19 or #20 or #21 or #22 or #23 or #24 or #27 or #30 or #33 or #34
36	#4 and #35

Databases: Embase, Medline, PsycINFO (OVID)
Date Range: inception to June 2017
Hits Deduped: 596 Undeduped: 710

- **Embase**

#	Searches
1	exp *multiple sclerosis/ or *myelitis/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
3	#1 or #2
4	cladribine/
5	(cladribin* or litak or leustat* or Biodribin or Hemobine or Intocel or Movectro).mp.
6	(2-Chloro-2'-deoxyadenosine or CdA or 2-CdA).mp.

#	Searches
7	#4 or #5 or #6
8	exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/
9	(clinical adj2 trial*).ti,ab.
10	(crossover or cross over).ti,ab.
11	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.
12	(placebo* or random*).ti,ab.
13	animals/ not human*.mp.
14	(or/#8-12) not #13
15	#3 and #7 and #14

- **Medline**

#	Searches
1	exp multiple sclerosis/ or myelitis, transverse/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
3	#1 or #2
4	Cladribine/
5	(cladribin* or litak or leustat* or Biodribin or Hemobine or Intocel or Movectro).mp.
6	(2-Chloro-2'-deoxyadenosine or CdA or 2-CdA).mp.
7	#4 or #5 or #6
8	exp clinical trial/ or exp "clinical trials as topic"/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/
9	(clinical adj2 trial*).ti,ab.
10	(crossover or cross over).ti,ab.
11	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.
12	(placebo* or random*).ti,ab.
14	#8 or #9 or #10 or #11 or #12
15	#3 and #7 and #13

- **PsychINFO**

#	Searches
1	exp multiple sclerosis/ or myelitis/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
3	#1 or #2
4	(cladribin* or litak or leustat* or Biodribin or Hemobine or Intocel or Movectro).mp.
5	(2-Chloro-2'-deoxyadenosine or CdA or 2-CdA).mp.
6	#4 or #5
7	(clinical trials or placebo or random sampling).sh,id.
8	(clinical adj2 trial*).ti,ab.
9	(crossover or cross over).ti,ab.
10	(((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).ti,ab.
11	(placebo* or random*).ti,ab.
12	treatment outcome*.md.
14	#7 or #8 or #9 or #10 or #11 or #12
15	#5 and #6 and #13

Review Question 4

Update of Rio 2016 review
Databases: PubMed, Medline, Embase, Web of SCIENCE
Date Range: Jan 2014 until December 2016
Hits Deduped: 1470 Undeduped: 1653

- Pubmed

#	**Searches**
1	((("Multiple Sclerosis"[Mesh]) OR ("Myelitis, Transverse"[Mesh:noexp]) OR ("Demyelinating Diseases"[Mesh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[Mesh:noexp]) OR ("Optic Neuritis"[Mesh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis")))
2	(("Interferon-beta"[Mesh]) OR ("Interferon-beta*") OR (rebif OR avonex OR betaseron OR betaferon)) OR ((copolymer-1 OR cop-1 OR copaxone OR “glatiramer acetate” OR glatiramer))
3	#1 AND #2
4	((response OR respond* OR failure OR non-respon* OR resist* OR fail* OR refractory) AND ((Expanded Disability Status Scale OR EDSS) OR (“magnetic resonance imaging” OR “MRI” OR “magnetic resonance” OR “MR” OR “nuclear magnetic resonance” OR “NMR”) OR relapse))
5	#3 AND #4
6	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tw] OR “clinical trials”[tw] OR “evaluation studies”[Publication Type] OR “evaluation studies as topic”[MeSH Terms] OR “evaluation study”[tw] OR evaluation studies[tw] OR “intervention studies”[MeSH Terms] OR “intervention study”[tw] OR “intervention studies”[tw] OR “cohort studies”[MeSH Terms] OR cohort[tw] OR “longitudinal studies”[MeSH Terms] OR “longitudinal”[tw] OR longitudinally[tw] OR “prospective”[tw] OR prospectively[tw] OR “follow up”[tw] OR “comparative study”[PT] OR “comparative study”[tw] OR systematic[subset] OR “meta-analysis”[PT] OR “meta-analysis as topic”[MeSH Terms] OR “meta-analysis”[tw] OR “meta-analyses”[tw]) NOT (Editorial[PT] OR Letter[PT] OR Case Reports[PT] OR Comment[PT]) NOT (animals[Mesh] NOT humans[Mesh])

#	Searches
7	#5 AND #6
8	((Epidemiologic Studies[Mesh:noexp] OR case-control studies[Mesh] OR cohort studies[Mesh] OR seroepidemiologic studies[Mesh]) OR cohort OR cohorts OR observ* OR case-control OR non-randomized OR nonrandomized OR unrandomized OR prospectiv* OR retrospectiv* OR follow* OR longitudinal OR (cases AND controls)) AND (odds ratio[Mesh] OR "odds ratio" OR "relative risk" OR risk OR risks OR associat* OR causality OR etiology OR epidemiology OR ethnology OR probability OR inciden*)
9	#5 AND #8
10	#7 OR #9

- Medline, Embase (SCOPUS)

#	Searches
1	TITLE-ABS-KEY ((("Multiple Sclerosis") OR ("Myelitis, Transverse") OR ("Demyelinating Diseases") OR ("Encephalomyelitis, Acute Disseminated") OR ("Optic Neuritis")) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis")))
2	TITLE-ABS-KEY ((("Interferon-beta") OR ("Interferon-beta*") OR (rebif OR avonex OR betaseron OR betaferon)) OR ((copolymer-1 OR cop-1 OR copaxone OR “glatiramer acetate” OR glatiramer)))
3	#1 AND #2
4	TITLE-ABS-KEY ((response OR respond* OR failure OR non-respon* OR resist* OR fail* OR refractory) AND ((Expanded Disability Status Scale OR EDSS) OR (“magnetic resonance imaging” OR “MRI” OR “magnetic resonance” OR “MR” OR “nuclear magnetic resonance” OR “NMR”)))
5	#3 AND #4
6	TITLE-ABS-KEY (“randomized controlled trial” OR “controlled clinical trial” OR randomized OR randomised OR randomization OR randomisation OR placebo OR “drug therapy” OR randomly OR trial OR groups OR “clinical trial” OR “clinical trials” OR “evaluation studies” OR “evaluation study” OR “intervention study” OR “intervention studies” OR cohort OR longitudinal OR longitudinally OR “prospective” OR prospectively OR “follow up” OR “comparative study” OR systematic OR “meta-analysis” OR “meta-analyses”) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "re") OR LIMIT-TO(DOCTYPE, "sh"))
7	#5 AND #6

#	Searches
8	TITLE-ABS-KEY ((“Epidemiologic Stud*” OR “seroepidemiologic stud*”) OR cohort OR cohorts OR observ* OR “case-control” OR non-randomized OR nonrandomized OR unrandomized OR prospectiv* OR retrospectiv* OR follow* OR longitudinal OR (cases AND controls)) AND ("odds ratio" OR "relative risk" OR risk OR risks OR associat* OR causality OR etiology OR epidemiology OR ethnology OR probability OR inciden*)
9	#5 AND #8
10	#7 OR #9

- Web of SCIENCE (Web of ScienceTM Core Collection, BIOSIS Previews®, MEDLINE®, Current Contents Connect)

#	Searches
1	TS = ((("Multiple Sclerosis") OR ("Myelitis, Transverse") OR ("Demyelinating Diseases") OR ("Encephalomyelitis, Acute Disseminated") OR ("Optic Neuritis")) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis")))
2	TS = ((("Interferon-beta") OR ("Interferon-beta*") OR (rebif OR avonex OR betaseron OR betaferon)) OR ((copolymer-1 OR cop-1 OR copaxone OR “glatiramer acetate” OR glatiramer)))
3	#1 AND #2
4	TS = ((response OR respond* OR failure OR non-respon* OR resist* OR fail* OR refractory) AND ((Expanded Disability Status Scale OR EDSS) OR (“magnetic resonance imaging” OR “MRI” OR “magnetic resonance” OR “MR” OR “nuclear magnetic resonance” OR “NMR”)))
5	#3 AND #4
6	TS = (“randomized controlled trial” OR “controlled clinical trial” OR randomized OR randomised OR randomization OR randomisation OR placebo OR “drug therapy” OR randomly OR trial OR groups OR “clinical trial” OR “clinical trials” OR “evaluation studies” OR “evaluation study” OR “intervention study” OR “intervention studies” OR cohort OR longitudinal OR longitudinally OR “prospective” OR prospectively OR “follow up” OR “comparative study” OR systematic OR “meta-analysis” OR “meta-analyses”)
7	#5 AND #6
8	TS = ((“Epidemiologic Stud*” OR “seroepidemiologic stud*”) OR cohort OR cohorts OR observ* OR “case-control” OR non-randomized OR nonrandomized OR unrandomized OR prospectiv* OR retrospectiv* OR follow* OR longitudinal OR (cases AND controls)) AND ("odds ratio" OR "relative risk" OR risk OR

#	Searches
	risks OR associat* OR causality OR etiology OR epidemiology OR ethnology OR probability OR inciden*)
9	#5 AND #8
10	#7 OR #9

Search for 'No Evidence of Disease Activity'
Databases: Embase, Medline, PsycINFO
Date Range: inception until January 2017
Hits Deduped: 244 Undeduped: 267

- Embase

#	**searches**
1	exp *multiple sclerosis/ or *myelitis/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
3	1 or 2
4	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
5	interferon beta serine.sh.
6	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
7	4 or 5 or 6
8	(beta1a interferon or recombinant interferon).sh.
9	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
10	8 or 9
11	peginterferon beta1a.sh.
12	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
13	11 or 12
14	glatiramer.sh.
15	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
16	14 or 15

17	teriflunomide.sh.
18	(aubagio or teriflunomid*).ti,ab.
19	17 or 18
20	fumaric acid dimethyl ester.sh.
21	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
22	20 or 21
23	fingolimod.sh.
24	(fingolimod* or gilenia or gilenya).ti,ab.
25	natalizumab.sh.
26	(antegren or natalizumab or tysabri).ti,ab.
27	23 or 24
28	25 or 26
29	alemtuzumab.sh.
30	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
31	29 or 30
32	daclizumab.sh.
33	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
34	32 or 33
35	mitoxantrone.sh.
36	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.
37	35 or 36
38	7 or 10 or 13 or 16 or 19 or 22 or 27 or 28 or 31 or 34 or 37
39	(evidence of disease activity or NEDA or EDA or disease free status or disease-free status).mp.
40	3 and 38 and 39

- Medline

#	**searches**
1	exp multiple sclerosis/ or myelitis, transverse/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.

#	searches
3	1 or 2
4	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
5	(interferon-beta or interferon type i).sh.
6	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
7	(interferon-beta or interferon type i).sh.
8	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
9	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
10	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
11	(aubagio or teriflunomid*).ti,ab.
12	fumarates.sh.
13	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
14	(fingolimod* or gilenia or gilenya).ti,ab.
15	(antegren or natalizumab or tysabri).ti,ab.
16	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
17	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
18	mitoxantrone.sh.
19	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.
20	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(evidence of disease activity or NEDA or EDA or disease free status or disease-free status).mp.
22	3 and 20 and 21

- PsychInfo

#	searches

#	searches
1	exp multiple sclerosis/ or myelitis/
2	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
3	1 or 2
4	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
5	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
6	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
7	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
8	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
9	(aubagio or teriflunomid*).ti,ab.
10	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
11	(fingolimod* or gilenia or gilenya).ti,ab.
12	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
13	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
14	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.
15	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	(evidence of disease activity or NEDA or EDA or disease free status or disease-free status).mp.
17	3 and 15 and 16

Review Question 6-8

Databases: Embase, Medline, PsycINFO
Date Range: inception to December 2015
Hits Deduped: 3779 Undeduped: 3853

#	searches
1	exp *multiple sclerosis/ or *myelitis/
2	1 use emez
3	exp multiple sclerosis/ or myelitis, transverse/
4	3 use mesz
5	exp multiple sclerosis/ or myelitis/
6	5 use psyh
7	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
8	or/56,58,60-61
9	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
10	interferon beta serine.sh. use emez
11	interferon-beta.sh. use mesz or interferon type i.sh. use mesz
12	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
13	or/64-66
14	beta1a interferon.sh. use emez or recombinant interferon.sh. use emez
15	interferon-beta.sh. use mesz or interferon type i.sh. use mesz
16	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
17	or/68-70
18	peginterferon beta1a.sh. use emez
19	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or

	(pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
20	or/72-73
21	glatiramer.sh. use emez
22	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
23	or/75-76
24	teriflunomide.sh. use emez
25	(aubagio or teriflunomid*).ti,ab.
26	or/78-79 (1940)
27	fumaric acid dimethyl ester.sh. use emez
28	fumarates.sh. use mesz
29	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
30	or/81-83
31	fingolimod.sh. use emez
32	(fingolimod* or gilenia or gilenya).ti,ab.
33	or/85-86
34	natalizumab.sh. use emez
35	(antegren or natalizumab or tysabri).ti,ab.
36	or/88-89
37	alemtuzumab.sh. use emez
38	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
39	or/91-92
40	daclizumab.sh. use emez
41	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
42	or/94-95
43	ocrelizumab.sh. use emez
44	(monoclonal antibod* or ocrelizumab or rhumab 2h7).ti,ab.
45	or/97-98
46	mitoxantrone.sh. use emez,mesz
47	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.

48	or/100-101
49	or/63,67,71,74,77,80,84,87,90,93,96,99,102
50	(switch* or cessat* or suspen* or stop* or withdraw* or interrupt* or discontin* or treatment strateg* or restart* or re-start* or initiate or de-escalat* or escalat* or second line or second-line).ti,ab.
51	62 and 103 and 104
52	remove duplicates from 105

Review Question 9

Databases: Embase, Medline, PsycINFO (OVID)
Date Range: inception to December 2016
Hits Deduped: 3066 Undeduped: 4323

#	Searches
1	exp *multiple sclerosis/ or *myelitis/
2	1 use emez
3	exp multiple sclerosis/ or myelitis, transverse/
4	3 use mesz
5	exp multiple sclerosis/ or myelitis/
6	5 use psyh
7	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
8	or/2,4,6-7
9	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
10	interferon beta serine.sh. use emez
11	interferon-beta.sh. use mesz or interferon type i.sh. use mesz
12	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab. (33090)
13	or/10-12 (49488)
14	beta1a interferon.sh. use emez or recombinant interferon.sh. use emez (8232)
15	interferon-beta.sh. use mesz or interferon type i.sh. use mesz (23192)
16	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab. (4334)
17	or/14-16 (34429)
18	peginterferon beta1a.sh. use emez (242)
19	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab. (466)
20	or/18-19 (590)
21	glatiramer.sh. use emez (6866)
22	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab. (5131)
23	or/21-22 (8947)
24	teriflunomide.sh. use emez (1683)
25	(aubagio or teriflunomid*).ti,ab. (912)
26	or/24-25 (1940)
27	fumaric acid dimethyl ester.sh. use emez (1967)
28	fumarates.sh. use mesz (4243)
29	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab. (1821)
30	or/27-29 (6570)
31	fingolimod.sh. use emez (6495)

32	(fingolimod* or gilenia or gilenya).ti,ab. (3841)
33	or/31-32 (7689)
34	or/9,13,17,20,23,26,30,33 (217637)
35	(clinically stable or clinically-stable or stable or clinical stability or clinical-stability or stability or long term or long-term).ti,ab. (3007791)
36	8 and 34 and 35 (4323)
37	remove duplicates from 36 (3066)

Review Question 10

Databases: Embase, Medline, PsycINFO (OVID)
Date Range: inception to December 2016
Hits Deduped: 808 Undeduped: 2033

#	Searches
1	exp *multiple sclerosis/ or *myelitis/
2	1 use emez
3	exp multiple sclerosis/ or myelitis, transverse/
4	3 use mesz
5	exp multiple sclerosis/ or myelitis/
6	5 use psyh
7	(((disseminated or insular or multiple or multiplex) adj2 scleros*) or chariot disease or encephalomyelitis disseminate or transverse myelitis).ti,ab. or ms.ti.
8	or/2,4,6-7
9	((disease adj2 modif* adj2 (agent* or drug* or therap* or treat*)) or ((immunomodulat* or immunosuppress* or (immun* adj (modulat* or suppress*))) adj2 (agent* or drug* or therap* or treat*))).ti,ab.
10	interferon beta serine.sh. use emez
11	interferon-beta.sh. use mesz or interferon type i.sh. use mesz
12	(beneseron or beta 1b interferon or beta1b interferon or beta interferon or betaferon or betaseron or extavia or fiblaferon or fibroblast interferon or ifnb or ifn b or ifn beta or ifnbeta or interferon beta or interferon fibroblast or rifn beta 1b or rifn beta1b).ti,ab.
13	or/10-12
14	beta1a interferon.sh. use emez or recombinant interferon.sh. use emez
15	interferon-beta.sh. use mesz or interferon type i.sh. use mesz)
16	(avonex or beta 1a interferon or beta1a interferon or cinnovex or ifn a or ifna or rebif or rifn beta).ti,ab.
17	or/14-16
18	peginterferon beta1a.sh. use emez
19	(beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta1a or (pegylated adj2 interferon beta 1a) or (pegylated adj2 interferon beta1a) or plegridy or (peginf or peg inf)).ti,ab.
20	or/18-19
21	glatiramer.sh. use emez
22	(cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or glatiramer or glatopa).ti,ab.
23	or/21-22
24	teriflunomide.sh. use emez
25	(aubagio or teriflunomid*).ti,ab.)
26	or/24-25
27	fumaric acid dimethyl ester.sh. use emez
28	fumarates.sh. use mesz
29	(dimethyl fumarate or dimetil fumarate or dimethylfumarate or dimetilfumarate or panaclar or tecfidera or trans butenedioic acid dimethyl ester or tecfidera).ti,ab.
30	or/27-29
31	fingolimod.sh. use emez
32	(fingolimod* or gilenia or gilenya).ti,ab.
33	or/31-32

34	natalizumab.sh. use emez
35	(antegren or natalizumab or tysabri).ti,ab.
36	or/34-35
37	alemtuzumab.sh. use emez
38	(alemtuzumab or campath or cd52 monoclonal antibody or emtrada or lemtrada or mabcampath or monoclonal antibody cd52).ti,ab.
39	or/37-38
40	daclizumab.sh. use emez
41	(daclizumab or dacliximab or dacluzimab or zenapax).ti,ab.
42	or/40-41
43	ocrelizumab.sh. use emez
44	(monoclonal antibod* or ocrelizumab or rhumab 2h7).ti,ab.
45	or/43-44
46	mitoxantrone.sh. use emez,mesz
47	(dhad or dhaq or domitrone or elsep or formyxan or misostol or mitoxanthron* or mitoxantron* or mitoxgen or mitozantron* or mitroxantron* or mitroxon* or neotalem or norexan or novanthron* or novantron* or oncotron* or onkotron* or quinizarin* or ralenova or pralifan*).ti,ab.
48	or/46-47
49	or/9,13,17,20,23,26,30,33,36,39,42,45,48
50	(Pregnan* or conception or child development or teratogen* or spermatozoa or ovum or reproduc* or birth or delivery or fetal or foetal or fetus or foetus or neonatal or obstetric* or abortion).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui, tc, id, tm]
51	8 and 49 and 50
52	limit 51 to yr="2012 -Current"
53	remove duplicates from 52

Appendix 3_References for excluded studies

Review questions 1-3

Reference	Reason for exclusion
Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernández O, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357(9268):1576-82.	Investigated an unlicensed dose of interferon
Demina TL, Khachanova NV, Davydovskaia MV. The interferon beta therapy after the first clinical episode of demyelination in multiple sclerosis. Zh Nevrol Psikhiatr Im S S Korsakova. 2006;106(3):15-9.	Non English language paper
Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, Smith S, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: A randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9444):1489-96.	Investigated an unlicensed dose of interferon
Hartung HP, Freedman MS, Polman CH, Edan G, Kappos L, Miller DH, et al. Interferon β-1b-neutralizing antibodies 5 years after clinically isolated syndrome. Neurology. 2011;77(9):835-43.	Trial already included. Outcomes reported not relevant
Nagtegaal GJ, Pohl C, Wattjes MP, Hulst HE, Freedman MS, Hartung HP, et al. Interferon beta-1b reduces black holes in a randomised trial of clinically isolated syndrome. Mult Scler. 2014;20(2):234-42.	Trial already included. Outcomes reported not relevant
Siddiqui MA, Wellington K. Intramuscular interferon-beta-1a: in patients at high risk of developing clinically definite multiple sclerosis. CNS Drugs. 2005;19(1):55-61; discussion 63-4.	Not a primary intervention study
De Stefano N, Sormani MP, Stubinski B, Blevins G, Drulovic JS, Issard D, et al. Efficacy and safety of subcutaneous interferon β-1a in relapsing-remitting multiple sclerosis: further outcomes from the IMPROVE study. J Neurol Sci. 2012;312(1-2):97-101.	16 week follow-up
Goodman AD, Rossman H, Bar-Or A, Miller A, Miller DH, Schmierer K, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. Neurology. 2009;72(9):806-12.	24 week follow-up
Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378(9805):1779-87.	24 week follow-up

Reference	Reason for exclusion
Cascione M, Wynn D, Barbato LM, Pestreich L, Schofield L, McCague K. Randomized, open-label study to evaluate patient-reported outcomes with fingolimod after changing from prior disease-modifying therapy for relapsing multiple sclerosis: EPOC study rationale and design. J Med Econ. 2013;16(7):859-65.	24 week follow-up
Comi G, O'Connor P, Montalban X, Antel J, Radue EW, Karlsson G, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler. 2010 ;16(2):197-207.	24 week follow-up
Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med. 2006;355(11):1124-40.	24 week follow-up
Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Effect of BG-12 on contrast-enhanced lesions in patients with relapsing--remitting multiple sclerosis: subgroup analyses from the phase 2b study. Mult Scler. 2012;18(3):314-21.	24 week follow-up
Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E, Limmroth V, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008;372(9648):1463-72.	24 week follow-up
Montalban X, Comi G, O'Connor P, Gold S, de Vera A, Eckert B, et al. Oral fingolimod (FTY720) in relapsing multiple sclerosis: impact on health-related quality of life in a phase II study. Mult Scler. 2011;17(11):1341-50.	24 week follow-up
Polman C, Barkhof F, Kappos L, Pozzilli C, Sandbrink R, Dahlke F, et al. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. Mult Scler. 2003;9(4):342-8.	24 week follow-up
Radue EW, O'Connor P, Polman CH, Hohlfeld R, Calabresi P, Selmaj K, et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. Arch Neurol. 2012;69(10):1259-69.	24 week follow-up
Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012;18(9):1269-77.	24 week follow-up
O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety	34 week follow-up

Reference	Reason for exclusion
and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006;66(6):894-900.	
Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001;49(3):290-7.	39 week follow-up
Rovaris M, Comi G, Rocca MA, Valsasina P, Ladkani D, Pieri E, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. Mult Scler. 2007;13(4):502-8.	39 week follow-up
Sormani MP, Bruzzi P, Comi G, Filippi M. The distribution of the magnetic resonance imaging response to glatiramer acetate in multiple sclerosis. Mult Scler. 2005;11(4):447-9.	39 week follow-up
Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry. 1997;62(2):112-8.	Combination of drugs
Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Ann Neurol. 2013;73(3):327-40.	Combination of drugs
Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):911-23.	Combination of drugs
Wynn D, Kaufman M, Montalban X, Vollmer T, Simon J, Elkins J, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010;9(4):381-90.	Combination of drugs
Fischer JS, Priore RL, Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. Ann Neurol. 2000;48(6):885-92.	Data not available
Cohen JA, Rovaris M, Goodman AD, Ladkani D, Wynn D, Filippi M. Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS. Neurology. 2007;68(12):939-44.	Dose comparison study

Reference	Reason for exclusion
Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M; FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. Ann Neurol. 2011;69(1):75-82.	Dose comparison study
Wolinsky JS, Borresen TE, Dietrich DW, Wynn D, Sidi Y, Steinerman JR, et al. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2015;4(4):370-6.	Dose comparison study
Bonavita S, Dinacci D, Lavorgna L, Savettieri G, Quattrone A, Livrea P, et al. Treatment of multiple sclerosis with interferon beta in clinical practice: 2-year follow-up data from the South Italy Mobile MRI Project. Neurol Sci. 2006;27 Suppl 5:S365-8.	Dose comparison trial
Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A,et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002;359(9316):1453-60.	Dose comparison trial
Freedman MS, Francis GS, Sanders EA, Rice GP, O'Connor P, Comi G, et al. Randomized study of once-weekly interferon beta-1la therapy in relapsing multiple sclerosis: three-year data from the OWIMS study. Mult Scler. 2005;11(1):41-5	Dose comparison trial
Mazdeh M, Afzali S, Jaafari MR. The therapeutic effect of Avonex, Rebif and Betaferon on EDSS and relapse in multiple sclerosis: a comparative study. Acta Med Iran. 2010;48(2):83-8.	Dose comparison trial
Mokhber N, Azarpazhooh A, Orouji E, Rao SM, Khorram B, Sahraian MA, et al. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: a randomized clinical trial. J Neurol Sci. 2014;342(1-2):16-20.	Dose comparison trial
Nafissi S, Azimi A, Amini-Harandi A, Salami S, shahkarami MA, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial. Clin Neurol Neurosurg. 2012;114(7):986-9.	Dose comparison trial
Oger J, Francis G, Chang P; PRISMS Study Group. Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: the PRISMS study. J Neurol Sci. 2005;237(1-2):45-52.	Dose comparison trial

Reference	Reason for exclusion
Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002;59(10):1496-506.	Dose comparison trial
Havrdova E, Zivadinov R, Krasensky J, Dwyer MG, Novakova I, Dolezal O. Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. Mult Scler. 2009;15(8):965-76.	Drug combination trial
Double-blind controlled trial of azathioprine in the treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry. 1987;50(10):1387.	Drug not licensed for MS
Double-masked trial of azathioprine in multiple sclerosis. British and Dutch Multiple Sclerosis Azathioprine Trial Group. Lancet. 1988;2(8604):179-83.	Drug not licensed for MS
Ellison GW, Myers LW, Mickey MR, Graves MC, Tourtellotte WW, Syndulko K, et al. A placebo-controlled, randomized, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. Neurology. 1989;39(8):1018-26.	Drug not licensed for MS
Massacesi L, Tramacere I, Amoroso S, Battaglia MA, Benedetti MD, Filippini G, et al. Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial. PLoS One. 2014;9(11):e113371.	Drug not licensed for MS
Mertin J, Knight SC, Rudge P, Thompson EJ, Healy MJ. Double-blind, controlled trial of immunosuppression in treatment of multiple sclerosis. Lancet. 1980;2(8201):949-51.	Drug not licensed for MS
Milanese C, La Mantia L, Salmaggi A, Campi A, Bortolami C, Tajoli L, et al. Double blind controlled randomized study on azathioprine efficacy in multiple sclerosis. Preliminary results. Ital J Neurol Sci. 1988;9(1):53-7.	Drug not licensed for MS
Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997;244(3):153-9.	Drug not prioritized for RRMS
Minderhoud JM1, Prange AJ, Luyckx GJ. A long-term double-blind controlled study on the effect of	Drug not licensed for MS

Reference	Reason for exclusion
azathioprine in the treatment of multiple sclerosis. Clin Neurol Neurosurg. 1988;90(1):25-8.	
Rivera VM, Jeffery DR, Weinstock-Guttman B, Bock D, Dangond F. Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) study. BMC Neurol. 2013;13:80.	Drug not prioritized for RRMS
Tindall RS, Walker JE, Ehle AL, Near L, Rollins J, Becker D. Plasmapheresis in multiple sclerosis: prospective trial of pheresis and immunosuppression versus immunosuppression alone. Neurology. 1982;32(7):739-43.	Drug not prioritized for RRMS
Csépány T. [Natalizumab retreatment: effectiveness and long-term safety in multiple sclerosis in the STRATA study]. Ideggyogy Sz. 2014;67(7-8):277-9.	Non English language paper
Demina TL, Khachanova NV, Davydovskaia MV, Popova NF, Gusev EI. [Clinical efficacy and safety of long-term immunomodulating therapy with interferon beta]. Zh Nevrol Psikhiatr Im S S Korsakova. 2008;108(4):24-6.	Non English language paper
Klotz L, Meuth SG, Kieseier B, Wiendl H. [Alemtuzumab for relapsing-remitting multiple sclerosis. Results of two randomized controlled phase III studies]. Nervenarzt. 2013;84(8):984-94.	Non English language paper
Komoly S. [Better life expectations of SM patients: 21 years follow up of patients treated with interferon beta-1b]. Ideggyogy Sz. 2013;66(3-4):143-4.	Non English language paper
López-Ruiz Minerva, Ruiz-Sandoval José Luis, Barroso-Rodríguez Noé Saúl, Cantú-Brito Carlos Gerardo, Violante-Villanueva José Arturo, Molina-Pérez Aarón, et al. Open label, extension-of-PRO-3209 trial to assess efficacy and safety of Probioglat® (glatiramer acetate) in Mexican patients with relapsing-remitting multiple sclerosis. Interim report of the first 12 months of treatment (Study PRO-4109). Rev Mex Neuroci. 2014;15(6):307-14.	Non English language paper
Magdolna S. [Effectiveness and safety of natalizumab in multiple sclerosis: data of the first five years from the TOP (Tysabri Observational Program)]. Ideggyogy Sz. 2014;67(5-6):211-2	Non English language paper
Popova EV, Boĭko AN, Davydovskaia MV, Demina TL, Kukel' TM, Lashch Niu, et al. [The first experience of the use the Russian B-interferon-1b biosimilar (infibeta) in the daily practice of the Moscow Center of Multiple Sclerosis]. Zh Nevrol Psikhiatr Im S S Korsakova. 2013;113(10 Pt 2):93-6.	Non English language paper

Reference	Reason for exclusion
Ruiz Sandoval José Luis, López-Ruiz Minerva, Barroso-Rodríguez Noé, Cantú-Brito Carlos, Violante-Villanueva Arturo, Hernández-Hernández Marisela, et al. Safety and pharmacodynamics comparative study to evaluate the effect of glatiramer acetate (Probioglat® and Copaxone®) study drug and reference over response Th1, Th2 and sVCAM in patients with Relapsing-Remitting Multiple Sclerosis. . Rev Mex Neuroci. 2013;14(6):306-13.	Non English language paper
Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997;244(3):153-9.	Drug not prioritized for RRMS
Minderhoud JM1, Prange AJ, Luyckx GJ. A long-term double-blind controlled study on the effect of azathioprine in the treatment of multiple sclerosis. Clin Neurol Neurosurg. 1988;90(1):25-8.	Drug not licensed for MS
Rivera VM, Jeffery DR, Weinstock-Guttman B, Bock D, Dangond F. Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) study. BMC Neurol. 2013;13:80.	Drug not prioritized for RRMS
Tindall RS, Walker JE, Ehle AL, Near L, Rollins J, Becker D. Plasmapheresis in multiple sclerosis: prospective trial of pheresis and immunosuppression versus immunosuppression alone. Neurology. 1982;32(7):739-43.	Drug not prioritized for RRMS
Csépány T. [Natalizumab retreatment: effectiveness and long-term safety in multiple sclerosis in the STRATA study]. Ideggyogy Sz. 2014;67(7-8):277-9.	Non English language paper
Demina TL, Khachanova NV, Davydovskaia MV, Popova NF, Gusev EI. [Clinical efficacy and safety of long-term immunomodulating therapy with interferon beta]. Zh Nevrol Psikhiatr Im S S Korsakova. 2008;108(4):24-6.	Non English language paper
Klotz L, Meuth SG, Kieseier B, Wiendl H. [Alemtuzumab for relapsing-remitting multiple sclerosis. Results of two randomized controlled phase III studies]. Nervenarzt. 2013;84(8):984-94.	Non English language paper
Komoly S. [Better life expectations of SM patients: 21 years follow up of patients treated with interferon beta-1b]. Ideggyogy Sz. 2013;66(3-4):143-4.	Non English language paper

Reference	Reason for exclusion
López-Ruiz Minerva, Ruiz-Sandoval José Luis, Barroso-Rodríguez Noé Saúl, Cantú-Brito Carlos Gerardo, Violante-Villanueva José Arturo, Molina-Pérez Aarón, et al. Open label, extension-of-PRO-3209 trial to assess efficacy and safety of Probioglat® (glatiramer acetate) in Mexican patients with relapsing-remitting multiple sclerosis. Interim report of the first 12 months of treatment (Study PRO-4109). Rev Mex Neuroci. 2014;15(6):307-14.	Non English language paper
Magdolna S. [Effectiveness and safety of natalizumab in multiple sclerosis: data of the first five years from the TOP (Tysabri Observational Program)]. Ideggyogy Sz. 2014;67(5-6):211-2	Non English language paper
Popova EV, Boĭko AN, Davydovskaia MV, Demina TL, Kukel' TM, Lashch Niu, et al. [The first experience of the use the Russian B-interferon-1b biosimilar (infibeta) in the daily practice of the Moscow Center of Multiple Sclerosis]. Zh Nevrol Psikhiatr Im S S Korsakova. 2013;113(10 Pt 2):93-6.	Non English language paper
Ruiz Sandoval José Luis, López-Ruiz Minerva, Barroso-Rodríguez Noé, Cantú-Brito Carlos, Violante-Villanueva Arturo, Hernández-Hernández Marisela, et al. Safety and pharmacodynamics comparative study to evaluate the effect of glatiramer acetate (Probioglat® and Copaxone®) study drug and reference over response Th1, Th2 and sVCAM in patients with Relapsing-Remitting Multiple Sclerosis. . Rev Mex Neuroci. 2013;14(6):306-13.	Non English language paper
Grieb P1, Stelmasiak Z. [Treatment of multiple sclerosis with cladribine (2-CDA), a new immunosuppressant agent. Theoretical basis and preliminary results]. Neurol Neurochir Pol. 1995 Jan-Feb;29(1):69-76.	Non English language paper
Cocco E, Marchi P, Sardu C, Russo P, Paolillo A, Mascia M, et al. Mitoxantrone treatment in patients with early relapsing-remitting multiple sclerosis. Mult Scler. 2007;13(8):975-80.	Not an RCT
Ghezzi A; Immunomodulatory Treatment of Early Onset MS (ITEMS) Group. Immunomodulatory treatment of early onset multiple sclerosis: results of an Italian Co-operative Study. Neurol Sci. 2005;26 Suppl 4:S183-6.	Not an RCT
Hamzehloo A, Etemadifar M. Mitoxantrone reduced disability in Iranian patients with multiple sclerosis. Arch Iran Med. 2007;10(1):59-64.	Not an RCT

Field Code Changed

Reference	Reason for exclusion
Lang C, Reiss C, Mäurer M. Natalizumab may improve cognition and mood in multiple sclerosis. Eur Neurol. 2012;67(3):162-6.	Not an RCT
Mattioli F, Stampatori C, Capra R. The effect of natalizumab on cognitive function in patients with relapsing-remitting multiple sclerosis: preliminary results of a 1-year follow-up study. Neurol Sci. 2011;32(1):83-8.	Not an RCT
McFarland HF. Alemtuzumab versus interferon beta-1a: implications for pathology and trial design. Lancet Neurol. 2009;8(1):26-8.	Not an RCT
Comi G, Hartung HP, Kurukulasuriya NC, Greenberg SJ, Scaramozza M. Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis Expert Opin Pharmacother. 2013 Jan;14(1):123-36.	Not an RCT
Khan O, Shen Y, Caon C, Bao F, Ching W, Reznar M, et al. Axonal metabolic recovery and potential neuroprotective effect of glatiramer acetate in relapsing-remitting multiple sclerosis. Mult Scler. 2005;11(6):646-51.	Pilot study (n=18)
Arnold DL, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study. J Neurol. 2014;261(9):1794-802.	Trial already included. No additional relevant outcomes
Miller DH, Fox RJ, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. Neurology. 2015;84(11):1145-52.	Trial already included. No additional relevant outcomes
Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007;68(17):1390-401.	Trial already included. No additional relevant outcomes
Arnold DL, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, et al. Magnetization transfer ratio in the delayed-release dimethyl fumarate DEFINE study. J Neurol. 2014;261(12):2429-37.	Trial already included. Outcomes reported not relevant
Arnold DL, Narayanan S, Antel S. Neuroprotection with glatiramer acetate: evidence from the PreCISe trial.	Trial already included.

Reference	Reason for exclusion
J Neurol. 2013;260(7):1901-6.	Outcomes reported not relevant
Cadavid D, Cheriyan J, Skurnick J, Lincoln JA, Wolansky LJ, Cook SD. New acute and chronic black holes in patients with multiple sclerosis randomised to interferon beta-1b or glatiramer acetate. J Neurol Neurosurg Psychiatry. 2009;80(12):1337-43.	Trial already included. Outcomes reported not relevant
Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012;11(5):420-8.	Trial already included. Outcomes reported not relevant
Graves J, Galetta SL, Palmer J, Margolin DH, Rizzo M, Bilbruck J, et al. Alemtuzumab improves contrast sensitivity in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2013;19(10):1302-9.	Trial already included. Outcomes reported not relevant
Kappos L, Giovannoni G, Gold R, Phillips JT, Arnold DL, Hotermans C, et al. Time course of clinical and neuroradiological effects of delayed-release dimethyl fumarate in multiple sclerosis. Eur J Neurol. 2015;22(4):664-71.	Trial already included. Outcomes reported not relevant
Kappos L, O'Connor PW, Polman CH, Vermersch P, Wiendl H, Pace A, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. J Neurol. 2013;260(5):1388-95.	Trial already included. Outcomes reported not relevant
Zivadinov R, Dwyer M, Barkay H, Steinerman JR, Knappertz V, Khan O. Effect of glatiramer acetate three-times weekly on the evolution of new, active multiple sclerosis lesions into T1-hypointense "black holes": a post hoc magnetic resonance imaging analysis. J Neurol. 2015;262(3):648-53.	Trial already included. Outcomes reported not relevant
Zivadinov R, Dwyer MG, Ramasamy DP, Davis MD, Steinerman JR, Khan O. The Effect of Three Times a Week Glatiramer Acetate on Cerebral T1 Hypointense Lesions in Relapsing-Remitting Multiple Sclerosis. J Neuroimaging. 2015;25(6):989-95.	Trial already included. Outcomes reported not relevant
Phillips JT, Giovannoni G, Lublin FD, O'Connor PW, Polman CH, Willoughby E, et al. Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis.	Trial already included. Post-hoc analysis not relevant

Reference	Reason for exclusion
Mult Scler. 2011;17(8):970-9.	
Uitdehaag B, Constantinescu C, Cornelisse P, Jeffery D, Kappos L, Li D, et al. Impact of exposure to interferon beta-1a on outcomes in patients with relapsing-remitting multiple sclerosis: exploratory analyses from the PRISMS long-term follow-up study. Ther Adv Neurol Disord. 2011;4(1):3-14.	Trial already included. Post-hoc analysis not relevant
Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Zhu Y, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 2014;14:240.	Trial already included. Sensitivity analysis not relevant
Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther. 2014;20(5):446-51.	Trial already included. Subgroup analyses not relevant
Cree BA, Stuart WH, Tornatore CS, Jeffery DR, Pace AL, Cha CH. Efficacy of natalizumab therapy in patients of African descent with relapsing multiple sclerosis: analysis of AFFIRM and SENTINEL data. Arch Neurol. 2011;68(4):464-8.	Trial already included. Sub-group analysis not relevant
Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X, et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol. 2013;260(8):2023-32.	Trial already included. Sub-set of included participants not relevant
Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Meltzer L, et al. Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with relapsing-remitting multiple sclerosis (RRMS). Mult Scler. 2015;21(1):57-66.	Trial already included. Sub-set of included participants not relevant
Rammohan K, Giovannoni G, Comi G, Cook S, Rieckmann P, Soelberg Sørensen P et al. Cladribine tablets for relapsing-remitting multiple sclerosis: Efficacy across patient subgroups from the phase III CLARITY study. Mult Scler Relat Disord. 2012 Jan;1(1):49-54.	No relevant outcomes
De Stefano N, Giorgio A, Battaglini M, De Leucio A, Hicking C, Dangond F. Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets. Mult Scler. 2017 Jan 1:1352458517690269.	No relevant outcomes
Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, Vermersch P. Sustained disease-activity-	No relevant outcomes

Reference	Reason for exclusion
free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol. 2011 Apr;10(4):329-37.	
Muir VJ1, Plosker GL. Cladribine tablets: in relapsing-remitting multiple sclerosis. CNS Drugs. 2011 Mar;25(3):239-49.	Descriptive review of CLARITY trial
Stelmasiak Z, Solski J, Nowicki J, Jakubowska B, Ryba M, Grieb P. Effect of parenteral cladribine on relapse rates in patients with relapsing forms of multiplesclerosis: res ults of a 2-year, double-blind, placebo-controlled, crossover study. Mult Scler. 2009 Jun;15(6):767-70.	Intervention not relevant
Rice GP, Filippi M, Comi G. Cladribine and progressive MS Clinical and MRI outcomes of a multicenter controlled trial. Neurology. 2000 Mar 14;54(5):1145-55.	Participants had progressive MS
Janiec K1, Wajgt A, Kondera-Anasz Z. Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic progressive multiple sclerosis. Med Sci Monit. 2001 Jan-Feb;7(1):93-8.	Participants had progressive MS
Selby R1, Brandwein J, O'Connor P. Safety and tolerability of subcutaneous cladribine therapy in progressive multiple sclerosis. Can J Neurol Sci. 1998 Nov;25(4):295-9.	Participants had progressive MS
Filippi M1, Rovaris M, Iannucci G, Mennea S, Sormani MP, Comi G. Whole brain volume changes in patients with progressive MS treated with cladribine. Neurology. 2000 Dec 12;55(11):1714-8.	Participants had progressive MS
Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. Proc Natl Acad Sci U S A. 1996 Feb 20;93(4):1716-20.	Participants had progressive MS

Review question 4-5

Reference	Reason for exclusion

Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Zhu Y, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 2014;14:240.	Comparison not relevant
Kappos L, De Stefano N, Freedman MS, Cree BA, Radue EW, Sprenger T, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. Mult Scler. 2016;22(10):1297-305.	Comparison not relevant
Damasceno A, Damasceno BP, Cendes F. No evidence of disease activity in multiple sclerosis: Implications on cognition and brain atrophy. Mult Scler. 2016;22(1):64-72.	No relevant data
Nygaard GO, Celius EG, de Rodez Benavent SA, Sowa P, Gustavsen MW, Fjell AM, et al. A longitudinal study of disability, cognition, and gray matter atrophy in early multiple sclerosis patients according to evidence of disease activity. PLoS One. 2015;10(8):e0135974.	No relevant data
Prosperini L, Fanelli F, Pozzilli C. Long-term assessment of No Evidence of Disease Activity with natalizumab in relapsing multiple sclerosis. J Neurol Sci. 2016;364:145-7.	No relevant data
Rio J, Rovira A, Blanco Y, Sainz A, Perkal H, Robles R, et al. Response to treatment with interferon beta in patients with multiple sclerosis. Validation of the Rio Score. Revista De Neurologia. 2016;63(4):145-150.	Non-English language paper

Review question 6

Reference	**Reason for exclusion**
Braune S, Lang M, Bergmann A; NTC Study Group. Second line use of Fingolimod is as effective as Natalizumab in a German out-patient RRMS-cohort. J Neurol. 2013;260(12):2981-5.	Comparison not relevant
Castillo-Trivino T, Mowry EM, Gajofatto A, Chabas D, Crabtree-Hartman E, Cree BA, et al. Switching multiple sclerosis patients with breakthrough disease to second-line therapy. PLoS One. 2011;6(2):e16664.	Comparison not relevant
Healy BC, Glanz BI, Stankiewicz J, Buckle G, Weiner H, Chitnis T. A method for evaluating	Comparison not relevant

Reference	Reason for exclusion
treatment switching criteria in multiple sclerosis. Mult Scler. 2010;16(12):1483-9.	
Carrá A, Onaha P, Luetic G, Burgos M, Crespo E, Deri N, et al. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing–remitting multiple sclerosis in Argentina. Eur J Neurol. 2008;15(4):386-93.	Drug not relevant
Caon C, Din M, Ching W, Tselis A, Lisak R, Khan O. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. Eur J Neurol. 2006;13(5):471-4.	No comparison group
Gajofatto A, Bacchetti P, Grimes B, High A, Waubant E. Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult Scler. 2009;15(1):50-8.	No relevant comparison
Kalincik T, Horakova D, Spelman T, Jokubaitis V, Trojano M, Lugaresi A, et al.; MSBase Study Group. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. Ann Neurol. 2015;77(3):425-35.	No relevant comparison
Lanzillo R, Bonavita S, Quarantelli M, Vacca G, Lus G, Amato L, et al. Natalizumab is effective in multiple sclerosis patients switching from other disease modifying therapies in clinical practice. Neurological Sciences. 2013;34(4):521-8.	No relevant comparison
Meng X, Chin PS, Hashmonay R, Zahur Islam M, Cutter G. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemp Clin Trials. 2015;41:69-74.	No relevant comparison
Putzki N, Yaldizli O, Maurer M, Cursiefen S, Kuckert S, Klawe C, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: Results from a multi-center study in German speaking countries. European Journal of Neurology. 2010;17(1):31-7.	No relevant comparison
Spelman T, Mekhael L, Burke T, Butzkueven H, Hodgkinson S, Havrdova E, et al. Risk of early relapse following the switch from injectables to oral agents for multiple sclerosis. European Journal of Neurology. 2016;23(4):729-36.	No relevant comparison

Reference	Reason for exclusion
Ziemssen T, Bajenaru OA, Carrá A, de Klippel N, de Sá JC, Edland A, et al. A 2-year observational study of patients with relapsing-remitting multiple sclerosis converting to glatiramer acetate from other disease-modifying therapies: the COPTIMIZE trial. J Neurol. 2014;261(11):2101-11.	No relevant comparison
Gajofatto A, Bianchi MR, Deotto L, Benedetti MD. Are natalizumab and fingolimod analogous second-line options for the treatment of relapsing-remitting multiple sclerosis? a clinical practice observational study. Eur Neurol. 2014;72(3-4):173-80.	Population not relevant (participants did not have to have evidence of disease activity and could be treatment naïve)

Review question 7

Reference	Reason for exclusion
Baumgartner A, Stich O, Rauer S. Clinical and radiological disease reactivation after cessation of long-term therapy with natalizumab. Int J Neurosci. 2012;122(1):35-9.	<10 participants per arm
Berger B, Baumgartner A, Rauer S, Mader I, Luetzen N, Farenkopf U, et al. Severe disease reactivation in four patients with relapsing-remitting multiple sclerosis after fingolimod cessation. J Neuroimmunol. 2015;282:118-22.	<10 participants per arm
Hakiki B, Portaccio E, Giannini M, Razzolini L, Pastò L, Amato MP. Withdrawal of fingolimod treatment for relapsing-remitting multiple sclerosis: report of six cases. Mult Scler. 2012;18(11):1636-9	<10 participants per arm
Havla J, Gerdes LA, Meinl I, Krumbholz M, Faber H, Weber F, et al. De-escalation from natalizumab in multiple sclerosis: recurrence of disease activity despite switching to glatiramer acetate. J Neurol. 2011;258(9):1665-9	<10 participants per arm
Gobbi C, Meier DS, Cotton F, Sintzel M, Leppert D, et al. Interferon beta 1b following natalizumab discontinuation: one year, randomized, prospective, pilot trial. BMC Neurol. 2013;13:101.	<10 participants per arm
Zecca C, Riccitelli GC, Calabrese P, Pravatà E, Candrian U, Guttmann CR, et al. Treatment satisfaction, adherence and behavioral assessment in patients de – escalating from natalizumab to interferon beta. BMC Neurol. 2014;14:38.	<10 participants per arm
Bianco A, Patanella AK, Nociti V, Marti A, Frisullo G, Plantone D, et al. Second-line therapy with fingolimod for relapsing-remitting multiple sclerosis in clinical practice: The effect of previous exposure to natalizumab. Eur Neurol. 2015;73(1-2):57-65	Comparison not relevant
Comi G, Gold R, Dahlke F, Sinha A, von Rosenstiel P, Tomic D. Relapses in patients treated with fingolimod after previous exposure to natalizumab. Mult Scler. 2015;21(6):786-90.	Comparison not relevant
Rieckmann P, Heidenreich F, Sailer M, Zettl UK, Zessack N, Hartung HP, et al. Treatment de-	Drug not prioritized for RRMS

Reference	Reason for exclusion
escalation after mitoxantrone therapy: Results of a phase IV, multicentre, open-label, randomized study of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis. Ther Adv Neurol Disord. 2012;5(1):3-12.	
Kappos L, Radue EW, Comi G, Montalban X, Butzkueven H, Wiendl H, et al. Switching from natalizumab to fingolimod: a randomized, placebo-controlled study in RRMS. Neurology. 2015;85(1):29-39.	No relevant comparison
O'Connor P, Goodman A, Kappos L, Lublin F, Polman C, Rudick RA, et al. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS study. Neurology. 2014;83(1):78-86.	No relevant comparison
Putzki N, Yaldizli O, Bühler R, Schwegler G, Curtius D, Tettenborn B. Natalizumab reduces clinical and MRI activity in multiple sclerosis patients with high disease activity: results from a multicenter study in Switzerland. Eur Neurol. 2010;63(2):101-6.	No relevant comparison
Stüve O, Cravens PD, Frohman EM, Phillips JT, Remington GM, von Geldern G, et al. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. Neurology. 2009;72(5):396-401.	No relevant outcomes
Capobianco M, di Sapio A, Malentacchi M, Malucchi S, Matta M, Sperli F, et al. No impact of current therapeutic strategies on disease reactivation after natalizumab discontinuation: a comparative analysis of different approaches during the first year of natalizumab discontinuation. Eur J Neurol. 2015;22(3):585-7.	NTZ < 12 months
Kaufman MD, Lee R, Norton HJ. Course of relapsing-remitting multiple sclerosis before, during and after natalizumab. Mult Scler. 2011;17(4):490-4.	NTZ < 12 months
Kerbrat A, Le Page E, Leray E, Anani T, Coustans M, Desormeaux C, et al. Natalizumab and drug holiday in clinical practice: an observational study in very active relapsing remitting multiple sclerosis patients. J Neurol Sci. 2011;308(1-2):98-102.	NTZ < 12 months
O'Connor PW, Goodman A, Kappos L, Lublin FD, Miller DH, Polman C, et al. Disease activity	NTZ < 12 months

Reference	Reason for exclusion
return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology. 2011;76(22):1858-65.	
Sorensen PS, Koch-Henriksen N, Petersen T, Ravnborg M, Oturai A, Sellebjerg F. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. J Neurol. 2014;261(6):1170-7.	NTZ < 12 months
Rossi S, Motta C, Studer V, De Chiara V, Barbieri F, Monteleone F, et al. Effect of glatiramer acetate on disease reactivation in MS patients discontinuing natalizumab. Eur J Neurol. 2013;20(1):87-94.	Population not relevant
Klotz L, Grützke B, Eveslage M, Deppe M, Gross CC, Kirstein L. Assessment of immune functions and MRI disease activity in relapsing-remitting multiple sclerosis patients switching from natalizumab to fingolimod (ToFingo-Successor). BMC Neurology. 2015;15:96.	Study protocol

Review question 8

Reference	Reason for exclusion
Sempere AP, Martin-Medina P, Berenguer-Ruiz L, Perez-Carmona N, Sanchez-Perez R, Polache-Vengud J, et al. Switching from natalizumab to fingolimod: An observational study. Acta Neurologica Scandinavica. 2013;128(2):e6-e10.	<10 participants per arm
Killestein J, Vennegoor A, Strijbis EM, Seewann A, Van Oosten BW, Uitdehaag BMJ, et al. Natalizumab drug holiday in multiple sclerosis: Poorly tolerated. Annals of Neurology. 2010;68(3):392-5.	<10 participants per arm
Barroso B, Miquel M, Marasescu R, Demasles S, Krim E, Bonnan M. Natalizumab is effective in controlling the inflammatory rebound after its discontinuation and failure of an alternative	Design not relevant. Case study

Reference	Reason for exclusion
treatment. Multiple Sclerosis and Related Disorders. 2015;4(4):380-2.	
Centonze D, Rossi S, Rinaldi F, Gallo P. Severe relapses under fingolimod treatment prescribed after natalizumab. Neurology. 2012;79(19):2004-5.	Design not relevant. Case study
Ghezzi A, Rocca MA, Baroncini D, Annovazzi P, Zaffaroni M, Minonzio G, et al. Disease reactivation after fingolimod discontinuation in two multiple sclerosis patients. J Neurol. 2013;260(1):327-9.	Design not relevant. Case study
Gunduz T, Kurtuncu M, Eraksoy M. Severe rebound after withdrawal of fingolimod treatment in patients with multiple sclerosis. Multiple Sclerosis and Related Disorders. 2017;11:1-3.	Design not relevant. Case study
Habek M. Severe relapse aft er stopping natalizumab for multiple sclerosis. Neurologia Croatica. 2014;63(1-2):61-2.	Design not relevant. Case study
Vecchio D, Naldi P, Stecco A, Cantello R, Leone MA. Severe rebound of spinal cord multiple sclerosis activity after fingolimod withdrawal. Clinical and Experimental Neuroimmunology. 2014;5(3):378-9.	Design not relevant. Case study
Ferrè L, Moiola L, Sangalli F, Radaelli M, Barcella V, Comi G, et al. Recurrence of disease activity after repeated Natalizumab withdrawals. Neurol Sci. 2015;36(3):465-7.	No relevant comparison
Lanzillo R, Bonavita S, Quarantelli M, Vacca G, Lus G, Amato L, et al. Natalizumab is effective in multiple sclerosis patients switching from other disease modifying therapies in clinical practice. Neurological Sciences. 2013;34(4):521-8.	No relevant comparison
Putzki N, Yaldizli O, Maurer M, Cursiefen S, Kuckert S, Klawe C, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: Results from a multi-center study in German speaking countries. European Journal of Neurology. 2010;17(1):31-7.	No relevant comparison
Fragoso YD, Alves-Leon SV, Becker J, Brooks JBB, Correa EC, Damasceno A, et al. Safety of switching from natalizumab straight into fingolimod in a group of JCV-positive patients with multiple sclerosis. Arquivos de Neuro-Psiquiatria. 2016;74(8):650-2.	No relevant outcomes

Reference	Reason for exclusion
Iaffaldano P, Viterbo RG, Trojano M. Natalizumab discontinuation is associated with a rebound of cognitive impairment in multiple sclerosis patients. J Neurol. 2016;263(8):1620-5.	No relevant outcomes
Laroni A, Brogi D, Milesi V, Abate L, Uccelli A, Mancardi GL. Early switch to fingolimod may decrease the risk of disease recurrence after natalizumab interruption. Multiple Sclerosis Journal. 2013;19(9):1236-7.	No relevant outcomes
Prosperini L, Annovazzi P, Capobianco M, Capra R, Buttari F, Gasperini C, et al. Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. Mult Scler. 2015;21(13):1713-22.	No relevant outcomes
Iuliano G, Napoletano R. Switching from drug to drug in multiple sclerosis: A longitudinal evaluation. Rivista Italiana di Neurobiologia. 2008;5(3):167-73.	Non-English language paper
Klotz L, Grutzke B, Eveslage M, Deppe M, Gross CC, Kirstein L, et al. Assessment of immune functions and MRI disease activity in relapsing-remitting multiple sclerosis patients switching from natalizumab to fingolimod (ToFingo-Successor). BMC Neurology. 2015;15(96).	Study protocol

Review question 9

Reference	Reason for exclusion
Kister I, Spelman T, Alroughani R, Lechner-Scott J, Duquette P, Grand'maison F, et al. Are stable MS patients who stop their disease-modifying therapy (DMT) at increased risk for relapses and disability progression compared to patients who continue on DMTs? A propensity-score matched analysis of the MSBase registrants. Multiple Sclerosis. 2015;1:17-18.	Same sample as Kister 2016

Review question 10

Reference	Reason for exclusion
Hellwig K, Gold R. Glatiramer acetate and interferon-beta throughout gestation and postpartum in women with multiple sclerosis. J Neurol. 2011;258: 502–503.	<10 participants per arm
Schneider H, Weber CE, Hellwig K, Schroten H, Tenenbaum T. Natalizumab treatment during pregnancy - effects on the neonatal immune system. Acta Neurol Scand. 2013;127(1):e1-4.	<10 participants per arm
Vukusic S, Durand-Dubief F, Benoit A, Marignier R, Frangoulis B, Confavreux C. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. Mult Scler. 2015;21(7):953-5.	<10 participants per arm
Fragoso YD, Finkelsztejn A, Comini-Frota ER, et al. Pregnancy and multiple sclerosis: the initial results from a Brazilian database. Arq Neuropsiquiatr. 2009;67:657– 660.	Case series design
Fragoso YD, Finkelsztejn A, Kaimen-Maciel DR, et al. Long-term use of glatiramer acetate by 11 pregnant women with multiple sclerosis: a retrospective, multicentre case series. CNS Drugs. 2010;24:969 –976.	Case series design
Finkelsztejn A, Fragoso YD, Ferreira ML, et al. The Brazilian database on pregnancy in multiple sclerosis. Clin Neurol Neurosurg. 2011;113:277–280	Case series design
Haghikia A, Langer-Gould A, Rellensmann G, Schneider H, Tenenbaum T, Elias-Hamp B, et al. Natalizumab use during the third trimester of pregnancy. JAMA Neurol. 2014;71(7):891-5.	Case series design
Salminen HJ, Leggett H, Boggild M. Glatiramer acetate exposure in pregnancy: preliminary safety and birth outcomes. J Neurol. 2011;257:2020 –2023.	Case series design
Sandberg-Wollheim M, Frank D, Goodwin TM, et al. Pregnancy outcomes during treatment with interferon -1a in patients with multiple sclerosis. Neurology. 2005;65:802–806	Case series design
Sandberg-Wollheim M, Alteri E, Stam Moraga M, Kornmann G. Pregnancy outcomes in	Case series design

multiple sclerosis following subcutaneous interferon beta-1a therapy. Mult Scler. 2011;17:423– 430.	
Sempere AP, Berenguer-Ruiz L, Feliu-Rey E. Rebound of disease activity during pregnancy after withdrawal of fingolimod. Eur J Neurol. 2013;20(8):e109-10.	Letter to the editor - no data available
Portaccio E, Ghezzi A, Hakiki B, Sturchio A, Martinelli V, Moiola L, et al. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. J Neurol Neurosurg Psychiatry. 2014;85(8):845-50.	No relevant outcomes
Hellwig K, Haghikia A, Gold R. Parenthood and immunomodulation in patients with multiple sclerosis. J Neurol. 2010;257:580 –583.	Population not relevant

Appendix 4_Characteristics of included studies

Review question 1. Treatment in CIS patients

Table 1:Interferon compared with placebo in CIS patients

Study ID (Trial name) N¥	FU†	Intervention groups	Age (mean)/ % female	EDSS (mean)‡	Disease duration*	% with mono-focal onset
Comi 2012 (REFLEX) N=517	104	1. Inteferon beta-1a (sc) 44 µg tiw 2. Placebo	31 64%	1.5	57.6 days from first demyelinating event	54%
Jacobs 2000 (CHAMPS) N=383	156	1. Interferon beta-1a (im) 30 µg qw 2. Placebo	33 75%	NR	NR	NR
Kappos 2006 (BENEFIT) N=468	104	1. Interferon beta-1b (sc) 250 µg (every other day) 2. Placebo	30 71%	1.5	NR	52%

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, * Mean length of time from first symptom at study baseline

Table 2: Characteristics of extension studies comparing early and delayed treatment with interferon in CIS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Kappos 2007 418 (89%)	3 years	Interferon beta-1b (250ug) SC every other day	BENEFIT	Early: 2.96 years (median) Delayed: 1 year (median)
Kappos 2009 392 (84%)	5 years	Interferon beta-1b (250ug) SC every other day	BENEFIT	Early: 5 years (median) Delayed: 2.9 years (median)
Edan 2014 284 (61%)	8 years	Interferon beta-1b (250ug) SC every other day	BENEFIT	Early: 7 years (median) Delayed: 4.5 years (median)
Kappos 2016 278 (59%)	11 tears	Interferon beta-1b (250ug) SC every other day	BENEFIT	NR
REFLEXION (NCT00813709) 155 (51.7%)	3 years, 5 years	Interferon beta-1a 44 µg (one a week or three times a week)	REFLEX	NR
Kinkel 2006 204 (53%)	5 years	Interferon beta-1a (30ug) IM once a week	CHAMPS	NR
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised				

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 3: Glatiramer acetate compared with placebo in CIS patients

Study ID (Trial name) N¥	FU†	Intervention groups	Age (mean)/ % female	EDSS (mean)‡	Disease duration*	% with mono-focal onset
Comi 2009 (PRECISE) 481	156	Glatiramer acetate (sc) 20mg/day Placebo	31.2 67%	1	74	100% mono-focal onset

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, * Mean length of time from first symptom at study baseline

Table 4: Extension studies comparing early and delayed treatment with glatiramer acetate in CIS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Comi 2013 409 (85%)	5 years	Glatiramer acetate 20mg/day	PRECISE	Early: 4.7 years (median) Delayed: 3.5 years (median)
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 5: Teriflunomide compared with placebo in CIS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease duration***	**% with mono-focal onset**
Miller 2014 (TOPIC) 413	108	1. Teriflunomide (14mg per day) 2. Placebo	32 67.7%	1.67	1.85 months since first neurological event	59.4%

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, * Mean length of time from first symptom at study baseline

Question 2: Treatment in RRMS and SPMS patients

Table 6: Interferon compared with placebo in relapsing MS patients

Study ID (Trial name) N¥	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Calabresi 2014 (ADVANCE) N=1516	48	1. Pegylated interferon beta 1-a 125 µg (every 2 weeks) 2. Placebo	37 71%	2.5	3.6	17%	1.66
IFNB MS Group 1993 N=383	156	1. Interferon beta-1b 1.6 MIU (every other day) 2. Placebo	36 85%	2.9	4.4	NR	3.4 (previous 2 years)
Jacobs 1996 (MSCRG) N=301	104	1. Interferon beta-1a 30 µg (qw) 2. Placebo	37 74%	2.4	6.5	NR	1.2
PRISMS1998 N=560	104	1. Interferon beta-1a 44µg (tiw) 2. Interferon beta-1a 22µg (tiw) 3. Placebo	35* 69%	2.5	5.3	NR	3 (previous 2 years)
Vollmer 2014** (BRAVO) N=1331	104	1. Interferon beta-1a 30 µg (qw) 2. Placebo	38* 70%	2.5*	1.3*	7.6%	1*

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values. **This trial also included a treatment arm of laquinimod which was not included in this review.

Table 7: Extension studies comparing early and delayed treatment with interferon in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Kieseier 2015 1332 (88%)	2 years	Peginterferon beta-1a (every 2 or 4 weeks)	ADVANCE	Early= 2 years Delayed= 1 year

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
PRISMS-4 506 (90%)	5 years	Interferon beta-1a (22µg or 44µg tiw)	PRISMS	NR
Kappos 2006 382 (68.2%) – at end of extension phase	7-8 years	Interferon beta-1a (22µg or 44µg tiw)	PRISMS	NR
Rudick 2005 172-218 (57%-72.4) efficacy/safety outcomes	8 years	Interferon beta-1a (30µg qwk)	MSCRG	Early= 4.2 years Delayed= 4.9 years
Ebers 2010 260 (69.9%)	16 years	Interferon beta-1b (50µg or 250µg qad)	IFNB Study Group	NR
Goodin 2012 366 (98.4%)	21 years	Interferon beta-1b (50µg or 250µg qad)	IFNB Study Group	NR
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial). Mean value unless specified otherwise.				

Table 8: Glatiramer acetate compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapses▼**
Fox 2012* (CONFIRM) N=1430	96	1. Glatiramer acetate (sc) 20mg/day 2. Placebo	37 70%	2.6	4.7	29%	1.4
Johnson 1995 (Copolymer 1 MS Study Group) N=383	104	1. Glatiramer acetate (sc) 20mg/day 2. Placebo	35 73%	2.6	6.9	NR	2.9 (previous 2 years)
Khan 2013 (GALA) N=1404	52	1. Glatiramer acetate (sc) 20mg/day 2. Placebo	38 68%	2.8	7.7	13.6%	1.3

¥ Total number of participants randomised in the trial, † Length of study follow-up in weeks, ‡ Mean baseline

score on the EDSS, ΔMean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *This trial also included two other treatment groups who received two doses of dimethyl fumarate.

Table 9: Extension studies comparing early and delayed treatment with glatiramer acetate in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Johnson 2000 208 (82.9%)	6 years	Glatiramer acetate 20mg/day	Copolymer 1 MS Study Group	Early= 5.8 years Delayed= NR
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 10: Teriflunomide compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Confavreux 2014 (TOWER) N=1169	104	1. Teriflunomide 14mg/day 2. Placebo	38 71%	2.7	8	33% (previous 2 years)	1.4
O'Connor 2011 (TEMSO) N=1088	108	1. Teriflunomide 14mg/day 2. Placebo	38 72%	2.7	8.7	27% (previous 2 years)	1.4

¥ Total number of participants randomised in the trial (includes unlicensed doses), † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values

Table 11: Extension studies comparing early and delayed treatment with teriflunomide in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
O'Conner 2016 742 (68.1%)	9 years	Teriflunomide (7mg)	TEMSO	Early = 5.7 years (median) Delayed = 3.7 years (median)
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of				

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 12: Dimethyl fumarate compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Fox 2012* (CONFIRM) N=1430	96	1. Dimethyl fumarate 240mg bid 2. Placebo	37 70%	2.6	4.67	29%	1.4
Gold 2012 (DEFINE) N=1237	104	1. Dimethyl fumarate 240mg bid 2. Placebo	38 74%	2.4	5.5	41%	1.3

¥ Total number of participants randomised in the trial (includes all treatment arms), † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. Fox 2012 also included a treatment arm investigating glatiramer acetate: see section 3.2.5.

Table 13: Extension studies comparing early and delayed treatment with dimethyl fumarate in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Gold 2016 1736 (66%)	5 years	Dimethyl fumarate 240mg (BID or TID)	DEFINE and CONFIRM	NR
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 14: Fingolimod compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**

Kappos 2010 (FREEDOMS) N=1272	104	1. Fingolimod 0.5mg/day 2. Placebo	37 70%	2.4	3.4	40%	1.47
Calabresi 2014b (FREEDOMS II) N=1083	104	1. Fingolimod 0.5mg/day 2. Placebo	41 78%	2.4	10.6	75%	1.47

¥ Total number of participants randomised in the trial (including all randomised treatment arms), † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

Table 15: Extension studies comparing early and delayed treatment with fingolimod in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Kappos 2015 920 (72%)	4-6 years	Fingolimod (0.5mg/day or 1.25mg/day)	FREEDOMS	Early (0.5mg)= 3.8 years Delayed= 1.8 years
NCT00355134 (unpublished) 632 (58.4%)	4.5 years	Fingolimod (0.5mg/day or 1.25mg/day)	FREEDOMS II	NR

†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial). Mean value unless specified otherwise.

Table 16: Natalizumab compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Polman 2006 N=942	104	1. Natalizumab 300mg (every 4 weeks) 2. Placebo	36 70%	2.3	5*	NR	1.52

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.
*Median values

Table 17: Daclizumab compared with placebo in relapsing MS patients

Study ID (Trial name) N¥	FU†	Intervention groups	Age (mean)/ % female	EDSS (mean)‡	Disease durationΔ	Prior treatment?◊	Number of relapsesΨ
Gold 2013 (SELECT) N=621	52	1. Daclizumab HYP (SC) 150mg (every 4 weeks) 2. Placebo	36 65%	2.7	2.7	24%	1.3

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

Table 18: Extension studies comparing early and delayed treatment with daclizumab in RRMS in relapsing MS patients

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Giovannoni 2014 517 (83%)	2 years	Daclizumab sc (150mg or 300mg q4w)	SELECT	Early= 2 years Delayed= 1 year
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Head to head comparisons

Table 19: Interferon compared to glatiramer acetate in relapsing MS patients

Study ID (Trial name) N¥	FU†	Intervention groups	Age (mean)/ % female	EDSS (mean)‡	Disease durationΔ	Prior treatment?◊	Number of relapsesΨ
Cadavid 2009 (BECOME) N=75	104	1. Interferon beta-1a (sc) 250µg (every other day) 2. Glatiramer acetate (sc) 20mg/day	36 69%	2*	1.1*	0%	1.9*
Calabrese 2012 N=383	104	1. Interferon beta-1a (sc) 44µg tiw 2. Interferon beta-1a (im) 30 µg qw 2. Glatiramer acetate (sc) 20mg/day	33 70%	1.9	5.5	0%	1.2
Mikol 2008	96	1. Interferon beta-1a (sc) 44µg tiw	37 70%	2.3	6.2	NR	NR

(REGARD) N=764		2. Glatiramer acetate (sc) 20mg/day					
O'Connor 2009 (BEYOND) N=560	104	1. Interferon beta-1a (sc) 250µg (every other day) 2. Glatiramer acetate (sc) 20mg/day	36 70%	2.3	5.3	0%	1.6

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values

Table 20: Teriflunomide compared with interferon in relapsing MS patients

Study ID **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Vermersch 2014 (TENERE) N=324	48	1. Teriflunomide 14mg/day 2. Interferon beta-1a (sc) 44µg tiw	36 68%	2.1	6.75	19% (previous 2 years)	1.3

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values

Table 21: Fingolimod compared with interferon in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Cohen 2010 (TRANSFORMS) N=1292	52	1. Fingolimod 0.5mg/day 2. Placebo	36 67%	2.2	7.3	57%	1.5

¥ Total number of participants randomised (including unlicensed doses), † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

Table 22: Daclizumab compared with interferon in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**

Kappos 2015 (DECIDE) N=1841	144	1. Daclizumab HYP (SC) 150mg (every 4 weeks) 2. Interferon beta-1a (im) 30 µg qw	36 65%	2.5	6.9	41%	1.6

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

Table 23: Alemtuzumab compared with interferon in relapsing MS patients

Study ID (Trial name) N¥	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
CAMMS223 2008 N=334	260	1. Alemtuzumab 12mg (yearly) 2. Interferon beta-1a 44µg tiw	32 64%	2	1.3*	0%	NR
Cohen 2012 (CARE MS-I) N=581	104	1. Alemtuzumab 12mg (yearly) 2. Interferon beta-1a 44µg tiw	33 65%	2.1	2.1	0%	1.47
Coles 2012 (CARE MS-II) N=840	104	1. Alemtuzumab 12mg (yearly) 2. Interferon beta-1a 44µg tiw	35 67%	2.7	4.5	Interferon beta or glatiramer for at least 6 months of treatment	1.6

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values

Table 24: Ocrelizumab compared with interferon in relapsing MS patients

Study ID (Trial name) N¥	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment?◊**	**Number of relapsesΨ**
Hauser 2017 (OPERA I 2016) N=821	96	1. Ocrelizumab 600mg (every 6 months) 2. Interferon beta-1a 44µg tiw	37 66%	2.84	1.8	73%	1.3
Hauser 2017	96	1. Ocrelizumab 600mg (every 6 months)	37 66%	2.8	1.9	74%	1.3

(OPERA II 2016) N=835		2. Interferon beta-1a 44µg tiw					

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year. *Median values

Table 25: Cladribine compared with placebo in relapsing MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age** **(mean)/** **% female**	**EDSS (mean)‡**	**Disease duration***	**% with mono-focal onset**
Giovannoni 2010 (CLARITY) 1326	96	1. Cladribine (4 courses of 3.5mg) 2. Cladribine (6 courses of 5.25mg) 3. Placebo	39 68%	2.9	8.7 years	NR

¥ Number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, * Mean length of time from diagnosis at study baseline

Table 26: Interferon compared with placebo in secondary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Number of relapsesΨ**
Andersen 2004 (Nordic SPMS Study Group) N=371	156	1. Interferon beta-1a (sc) 22 µg qw 2. Placebo	46 60%	4.8	14.3	1.7
North American Study Group 2004 N=939	156	1. Interferon beta-1b (sc) 250 µg (every other day) 2. Placebo	47 62%	5.1	14.7	0.8 (previous 2 years)
SPECTRIMS 2001 N=618	156	1. Interferon beta-1a (sc) 44µg tiw 2. Interferon beta-1a (sc) 22µg tiw 3. Placebo	43 63%	5.4	13.3	0.9 (previous 2 years)
The European Study Group 1998 N=718	156	1. Interferon beta-1b (sc) 8MIU 2. Placebo	41 61%	5.1	13	NR

¥ Total number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

Table 27: Extension studies comparing early and delayed treatment with interferon in secondary progressive MS

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Kuhle 2016 484 (67.4%)	10 years	Interferon beta-1b (sc) 8MIU	The European Study Group 1998	At Year 10 there were 120 patients (33%) on IFNB-1b; 160 (44%) had no treatment
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 28: Mitoxantrone compared with placebo in secondary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Number of relapsesΨ**
Hartung 2002 (MIMS) N=194	104	1. Mitoxantrone 12mg/m^2 (every 3 months) 2. Placebo	40 48%	4.6	10	1.29

¥ Total number of participants randomised including unlicensed dose. Data from 124 participants included in this review. † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug, Ψ Mean number of relapses in the previous year.

<u>Question 3: Treatment in PPMS patients</u>

Table 29: Interferon compared with placebo in primary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment◊**
Leary & Thompson 2003 N=50	104	1. Interferon beta-1a (im) 30µg qw 2. Placebo	45 36%	5.2	8	NR
Montalban 2004 N=73	104	1. Interferon beta-1b (sc) 8MIU (every other day) 2. Placebo	49 50%	5.2	11.4	0%

¥ Total number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug

Table 30: Characteristics of extension studies comparing early and delayed treatment with interferon in PPMS

Study ID N (% of original cohort)†	Length of follow-up*	Drug	Original trial/study ID	Length of exposure‡
Tur 2011 63 (86%)	7 years	Interferon beta-1b (sc) 8MIU (every other day)	Montalban 2004	All patients were drug free during extension
†Number of participants at start of the extension phase, *Length of follow-up from original study baseline to end of extension study, ‡Length of exposure to investigational drug in the early treatment group (participants randomised to the investigational drug during the core trial) and in the delayed treatment group (participants who were not originally randomised to the investigational drug during the core trial).				

Table 31: Glatiramer acetate compared with placebo in primary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment◊**
Wolinsky 2007 N=943	156	1. Glatiramer acetate 20mg/ day 2. Placebo	50 51%	4.9	5	NR

¥ Total number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug

Table 32: Interferon compared with placebo in primary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment◊**
Lublin 2016 N=970	156	1. Fingolimod 0.5mg/day 2. Placebo	49 48%	4.7	2.9	22%

¥ Total number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug

Table 33: Ocrelizumab compared with placebo in primary progressive MS patients

Study ID **(Trial name)** **N¥**	**FU†**	**Intervention groups**	**Age (mean)/ % female**	**EDSS (mean)‡**	**Disease durationΔ**	**Prior treatment◊**
Montalban 2017 (ORATORIO 2015) N=732	120	1. Ocrelizumab 600mg (every 6 months) 2. Placebo	45 49%	4.7	3.2	12%

¥ Total number of participants randomised, † Length of study follow-up in weeks, ‡ Mean baseline score on the EDSS, Δ Mean number of years from diagnosis at study baseline, ◊ Proportion of participants who had received previous treatment with a disease modifying drug

Question 4: Monitoring treatment response

Table 34: Characteristics of Rio 2016

Study ID (last year searched)	**Aim of the review**	**No. studies /criteria**	**Inclusion/exclusion criteria**	**Criteria¥**
Rio 2016 (2014)	To examine the predictive value of short-term suboptimal response criteria for long-term non-response	k=45* Cr=29*	(1) ≥18 years (2) RRMS diagnosis (3) treated with IFNb or GA (4) ≥1 *short-term* suboptimal response criteria† measured post-treatment initiation (max 24 months after treatment initiation) (5) ≥1 *long-term* efficacy outcome‡ (measured ≥24 months from treatment initiation)	1. Gd ≥1 2. New T2 ≥1 3. New T2 ≥2 4. New T2 ≥3 5. MRI >2 6. R>1 7. ΔEDSS 8. ΔEDSS ≥1/1.5 and R≥1 9. Canadian TOR 10. MRI >2 and R≥1 11. ModRIO ≥2 12. ΔEDSS ≥1/1.5 and MRI>2 13. MRI>2 + [ΔEDSS ≥1/1.5 or R≥1) 14. RIO ≥1 15. RIO ≥2 16. RIO ≥3
Canadian TOR - Canadian treatment optimization recommendations, Cr – number of short-term criteria evaluated; DOR – diagnostic odds ratio, Gd – number of gadolinium enhanced lesions, k – number of included studies, ModRIO – modified RIO score, MRI – number of active magnetic resonance imaging scans, n – number of included participants, T2 - number of new or enlarging T2-weighted lesions, R – number of relapses, RIO – the RIO score, ΔEDSS – increase in EDSS score, † Including at least EDSS and/or MRI parameters and/or relapse rate. Only conventional MRI parameters (gadolinium-enhancing (Gd+) lesions, T2-weighted lesions and T1 hypointense lesions) were considered. ‡EDSS progression between 2 and 5 years after treatment initiation, defined as an increase in EDSS ≥ 1 (or EDSS ≥ 1.5 for baseline EDSS=0 and/or ≥0.5 for baseline EDSS>5.0). *16 studies and criteria included in meta-analyses. ¥Criteria assessed in more than 1 cohort which were included in the meta-analysis. ΨAssessed with the AMSTAR (Assessing the Methodological Quality of Systematic Reviews). § E.g. relapse rate or sustained increase in EDSS score				

Table 35: Characteristics of studies from the updated search

Study ID N†/FU‡	**Design**	**Where were participants selected from?**	**Treatment**	**Criteria assessed**	**Outcome**
Hyun 2015 n=70 FU= 3 years	Retrospective cohort	10 referral hospitals in Korea	Interferon-β	**Rio Score** (≥2) **Modified Rio Score** (≥2)	Clinical relapse and/or disability worsening (EDSS change ≥1 for EDSS<6 or ≥0.5 for EDSS≤6 at 1 year)
Romeo 2015 n=416 FU= 5 years	Retrospective cohort	Single MS centre in Italy	Interferon-β	**Rio Score** (≥2) **Modified Rio Score** (≥2)	Disability worsening (EDSS progression ≥1.0 point sustained at least 6 months or

Study ID N†/FU‡	Design	Where were participants selected from?	Treatment	Criteria assessed	Outcome
					EDSS progression ≥1.5 points if baseline EDSS <2.5 and 1 point if baseline EDSS was 2.5–5.5 sustained over at least 6 months) or switching to second-line drug
Sormani 2016* N= 1,280	Retrospective cohort	Integrated dataset of patients from 10 MAGNIMS centers	Interferon-β	**MAGNIMS** (group 2)	Disability worsening (0.5 point if baseline EDSS ≥5.5 and 1.5 points if baseline EDSS=0) or switching to other therapies due to lack of efficacy
†Number of participants at baseline, ‡ Length of study follow-up, *Includes data from Romeo 2015. NEDA – no evidence of disease activity Definitions: **NEDA** - absence of (a) relapse, (b) sustained disability worsening, or (c) MRI activity; **Rio Score ≥2** - presence of 2 or more of: (a) relapse, (b) sustained disability worsening, or (c) MRI activity; **Modified Rio Score ≥2** – (a) ≤4 new T2 lesions and ≥2 relapses, (b) >4 new T2 lesions and 1 relapse, or (c) >4 new T2 lesions and ≥2 relapses, **MAGNIMS group 2 -** 1 relapse and ≥3 new T2 lesions or ≥2 relapses					

Table 36: Characteristics of Rottstein 2015

Study ID N†/FU‡	Design	Where were participants selected from?	Treatment	Criteria assessed	Outcome
Rottstein 2015 n=219 FU= 7 years	Prospective cohort	Partners Multiple Sclerosis Center CLIMB study	48% receiving no treatment 36% on interferon 15% of glatiramer acetate 1% on other DMTs	**NEDA**	Absence of disability worsening (EDSS change ≤0.5)
†Number of participants at baseline, ‡ Length of study follow-up **NEDA** – no evidence of disease activity. Defined as absence of: (a) relapse, (b) sustained disability worsening, or (c) MRI activity;					

<u>Question 6: Treatment strategy if inadequate treatment response</u>

Table 37: Characteristics of RCTs included for Review Question 6

Study ID N†/FU‡	Design	Treatment before switch	Switched to		Risk of bias
			Group 1	Group 2	

Cohen 2013 n=613 FU= 52	RCT	Interferon	Fingolimod	Interferon	Low risk for all domains.
Coles 2012 n=637 FU=104	RCT	Interferon or glatiramer acetate	Alemtuzumab	Interferon	High risk of performance and detection bias. Low risk for all other domains.
EPOC 2014 (NCT01216072) n=1053 FU=24	RCT	Interferon or glatiramer acetate	Fingolimod	Any iDMT	High risk of performance and detection bias. Low risk for all other domains.

†Number of participants at the start of the study, ‡Length of follow-up in weeks after the switch

Table 38: Characteristics of cohort studies included for Review Question 6

Study ID N†	Design	Where were participants selected from?	Treatment before switch	Switched to		Risk of bias
				Group 1	Group 2	
Bergvall 2014 n=264 FU= 51	Retrospective cohort	US health insurance claims database	Interferon	Fingolimod	Glatiramer acetate	Serious risk
Braune 2016 n=198 FU= 104	Retrospective cohort	NeuroTransData network	Interferon or glatiramer acetate	Fingolimod	Any iDMT	Moderate risk
He 2015 n=527 FU=104	Retrospective cohort	MSBase registry	Interferon or glatiramer acetate	Fingolimod	Any iDMT or remain on same drug	Moderate risk
Prosperini 2012 n=285 FU=104	Prospective cohort	MS centres	Interferon or glatiramer acetate	Any second line (all ended on Natalizumab)	Any iDMT	Serious risk
Rio 2012 n=180 FU= ~219	Retrospective cohort	Neuroimmunology Clinic	Interferon or glatiramer acetate	Any second line (natalizumab and mitoxantrone)	Any iDMT	Serious risk
Spelman 2015 n= FU=104	Retrospective cohort	MSBase registry and TYSABRI Observational Program	Interferon or glatiramer acetate	Natalizumab	Any iDMT	Moderate risk

†Number of participants at the start of the study, ‡Length of follow-up in weeks after the switch

Treatment strategy if safety isues

Table 39: Characteristics of studies included for Review Question 7

Study ID N† FU	Design	Length of NTZ treatment	Therapy post-NTZ	Definition of rebound	Wash-out	Quality
Weinstock-Guttman 2015 n=50 FU= 52	RCT	41 doses	Interferon, GA, fingolimod, dimethyl fumatate or teriflunomide at 1–6 months following the last natalizumab infusion. Tapered group were administered two additional natalizumab infusions, one at 6 weeks and one at 8 weeks (14 weeks from study entry)	Not defined	1-2 months for iDMTs 3-6 months for oral DMTs)	Fair
Borriello 2011 N=21 FU=15	Prospective cohort	24 doses	Corticosteroids for relapses	Not defined	n/a	Poor
Borriello 2012 n= 23 FU= 15	Prospective cohort	19 doses	None	Not defined	n/a	Fair
Clerico 2014 n=130 FU= 52	Prospective cohort	NR	65.3% stopped natalizumab therapy Alternative DMTs were: interferon beta, GA or fingolimod 34.7% continued natalizumab	Not defined	None except for those switching to fingolimod (3 months)	Good
Cohen 2014 n=333 FU= 6 months	Prospective cohort	31 doses	Fingolimod	Not reported	Varied	Fair
Evangelopoulos 2016 n=30 FU= 26	Prospective cohort	44 doses	20/30 participants received monthly 1000 mg methylprednisolone (MPD) intravenously 10/30 participants received no treatment	Not reported	None	Poor
Hatcher 2016 n=46 FU= 104	Prospective cohort	NR	NR	New severe neurological symptoms after ceasing fingolimod treatment with the	NR	Poor

Study ID N† FU	Design	Length of NTZ treatment	Therapy post-NTZ	Definition of rebound	Wash-out	Quality
				development of multiple new or enhancing lesions exceeding baseline activity.		
Miravalle 2011 n=32 FU= 17	Prospective cohort	17 doses	None	Not reported	n/a	Fair
West & Cree 2010 n=68 FU= 24	Prospective cohort	NR	None	Return of disease activity and unusually severe flares (who had a severe flare, with a nearly 3-point increase in median EDSS score accompanied by a large number of gadolinium-enhancing lesions and associated with limited recovery of neurological function)	n/a	Fair
Gueguen 2014 n=32 FU= 52	Prospective cohort	28 months (mean of medians)	25% received no treatment 19% received interferon-beta (started within 1 month) or glatiramer acetate (started immediately)	Several relapses (three to four) and EDSS score increase (1.5–3.5).	0-1 month	Poor
Magraner 2011 n=18 FU= 46	Prospective cohort	24 months	Daily glatiramer acetate (20ug SC)	dramatic clinical and radiological worsening, which appears soon after NTZ therapy discontinuation	3 months	Fair
Rossi 2014 n=105 FU= 26	Prospective cohort	NR	Participants who previously did not respond to interferon, were switched to GA, and those previously not responding to GA were switched to IFN. As the	An increase in disease activity following NTZ dosage interruption (at least 4 T1 Gd+ lesions more	None	Fair

Study ID N† FU	Design	Length of NTZ treatment	Therapy post-NTZ	Definition of rebound	Wash-out	Quality
			first 40 patients treated with GA showed suboptimal disease control, pulse steroids were added for subsequent participants (intravenous 1000 mg methylprednisolone every month for three consecutive months)	than in pre-NTZ scans)		
Sangalli 2014 n=110 FU= 52	Prospective cohort	24 courses	82% started immunomodulant therapy, either glatiramer acetate (n=72) or interferon beta (n=18) within approximately one month after last infusions 9% started therapy with fingolimod after a mean of 4.6 months (3-6) 9% did not start any DMT	At least one of the following features: (a) clinically significant increase (at least 2-fold) of ARR in comparison to pre-NTZ disease course; (b) one or more severe relapses with sustained disability progression; (c) 5 or more new large T2 lesions and/or at least 10 more Gd-enhancing lesions than pre-NTZ baseline scan.	3-6 months (mean=4.6)	Fair
Havla 2013 n=36 FU= 52	Retrospective cohort	27 doses (median)	72% switched to fingolimod 28% were therapy free	Not reported	3.15 (median) months for fingolimod group	Fair
Lo Re 2015 n=132 FU= 52	Retrospective cohort	25 doses (median)	28% therapy free 7% restarted natalizumab 43% started fingolimod 12% started first-line therapies 3% other immunosuppresive treatment 5.4% rituximab 1.5% AHSCT	At least two of the following features was arbitrarily decided: 1. An ARR increase in comparison to pre-NTZ disease course; 2. One or more severe relapses with sustained disability	5 months (median)	Fair

Study ID N† FU	Design	Length of NTZ treatment	Therapy post-NTZ	Definition of rebound	Wash-out	Quality
				progression (one-step EDSS increase); 3. Three or more new large T2 lesions and/or Gd-enhancing lesions in the MRI; 4. New tumor-like demyelinating lesions in the MRI.		
Melis 2014 n=54 FU= 52	Retrospective cohort	21 months	23% refused treatment 77% received DMD (20% immunomodulators, 9% immunosuppresives, 4% fingolimod) 44% eventually re-started natalizumab	Change in the disease course with worsening of the disease activity beyond the pre-treatment levels.	3 months (for participants who started another DMD) 4 months (for participants who re-started NTZ)	Poor
Rinaldi 2012 n=22 FU= 39	Retrospective cohort	32 doses	Fingolimod	Not defined	3 months	Poor
Salhofer-Polanyi 2014 n=201 FU= 52	Retrospective cohort	25 months	33% switched to fingolimod, 14% switched to glatiramer acetate, 7% re-started natalizumab, 4% tried more than one treatment	clinical worsening beyond pretreatment levels and was measured by mean change scores of ARR and EDSS. MRI data were also collected, and progression on MRI was defined as an increase in gadolinium-enhancing lesions and T2 lesion	0-3 month (58%) >3 months (29%)	Poor

Study ID N† FU	Design	Length of NTZ treatment	Therapy post-NTZ	Definition of rebound	Wash-out	Quality
				load.		
Vidal-Jordana n=47 FU= 52	Retrospective cohort	23 months	70% were started on another DMD	Significant clinical worsening was defined as a 2-step EDSS increase (at least a 2-point increase in the last follow-up EDSS, in patients with an EDSS score upon natalizumab discontinuation of <5.5, or an increase of at least 1 point, in patients with an EDSS score upon natalizumab discontinuation of ≥5.5), 6–12 months after natalizumab withdrawal.	6.82 months	Fair

Table 40: Characteristics of studies included for Review Question 8

Study ID N†/FU‡	Design	Where were participants selected from?	Treatment before switch (mean doses)	Switched to			Risk of bias
				Group 1	Group 2	Group 3	
Alping 2016 n=256 FU	Prospective cohort	Three MS centres in Sweden	Natalizumab (41 doses*)	Rituximab	Fingolimod	n/a	Moderate risk
Fox 2014 n=175 FU= 28	RCT	Clinical trial	Natalizumab (28 doses*)	Natalizumab	Placebo	IFN, GA, MPL	High risk
Iaffaldano 2015 n=214 FU= 52	Prospective cohort	iMedWeb registry	Natalizumab (24 doses)	Fingolimod	Any iDMT	n/a	Moderate risk
Sangalli 2014 n=110 FU= 52	Prospective cohort	Outpatients at the San Raffaele MS Center in Milan	Natalizumab (24 doses)	Fingolimod	Any iDMT	No treatment	Serious risk

†Number of participants at the start of the study, ‡Length of follow-up in weeks after the switch, * mean of medians

GA – glatiramer acetate, IFN – interferon, iDMT – any injectable disease modifying therapy excluding natalizumab, MPL – methylprednisolone, n/a – not applicable

Question 10: Treatment in special situations: pregnancy

Table 41: Outcomes of studies including women exposed to interferon

Study_ID	Country	N	Study design	Type of drug exposed to	Average gestational duration of exposure
Amato 2010	Italy	415	Prospective cohort	Interferon beta	4.6 weeks
Boscovic 2005	Canada	46	Prospective cohort	Interferon beta	9 weeks
Coyle 2014	USA	99	Prospective cohort	Interferon beta	NR

Romero 2015	Worldwide	423	Prospective cohort	Interferon beta	NR
Thiel 2016	Germany	445	Prospective cohort	Interferon beta	median = 32 days
Herbstritt 2016	Germany	246	Prospective cohort	Glatiramer acetate	median = 31 days
Giannini 2012	Italy	415	Prospective cohort	Interferon beta and glatiramer acetate	IFNB = 4.6 weeks GA = 4.9 weeks
Weber-Schoendorfer & Schaefer 2009	Germany	NR	Prospective cohort	Interferon beta and glatiramer acetate	IFN : 8.8 wk (median) - 50% beyond week 6, 25% beyond week 9 GA: 6.9 wk (median) - 50% beyond week 6, 25% beyond week 7
Ebrahimi 2015	Germany	179	Prospective cohort	Natalizumab. Interferon beta and glatiramer acetate.	Natalizumab: 100% exposed at some point during pregnancy Disease matched: 32% on 1st line drugs exposed at some point during pregnancy
Hellwig 2011	Germany	NR	Prospective cohort	Natalizumab	6 women received the last infusion prior to last menstrual period 29 received last infusion after last menses
Hellwig 2012	Germany	335	Retrospective + prosepctive cohort	Interferon beta and glatiramer acetate	IFNB: 8.8 weeks GA: 6.5 weeks
De La Heras 2007	Spain	74	Retrospective cohort	Immunomodulatory therapy	5.44 weeks
Fernandez Liguori 2009	Argentina	81	Retrospective cohort	Interferon beta and glatiramer acetate	4 weeks since conception
Lu 2012	Canada	311	Retrospective cohort	Interferon beta and glatiramer acetate	7.2 weeks
Fragoso 2013	Argentina, Brazil, Mexico, UK	132	Retrospective cohort	Interferon, glatiramer acetate, pulses of immunoglobulin, high-dose oral corticosteroids	18.4 weeks
Gold 2015	Multiple	NR	Retrospective cohort	Dimethyl fumarate	Not reported

Karlsson 2014	Multiple	89	Retrospective cohort	Fingolimod	8-12 weeks in utero exposure in 83% (n=55) >12 weeks exposure in utero for 5 pregancies
Kieseier & Benamor 2014	Multiple	NR	Retrospective cohort	Teriflunomide	Not reported
Patti 2008	Italy	38	Retrospective cohort	Interferon beta	9.1 weeks

Appendix 5_GRADE tables

Review question 1

1. **Interferon compared with placebo for clinically isolated syndrome**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Placebo	Relative (95% CI)	Absolute		
Time to conversion to CDMS (104 weeks' follow-up) (follow-up mean 104 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.49 (0.38 to 0.64)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Conversion to CDMS (follow-up 104-156 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/363 (41.9%)	217/360 (60.3%)	RR 0.71 (0.61 to 0.82)	175 fewer per 1000 (from 109 fewer to 235 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								61.6%		179 fewer per 1000 (from 111 fewer to 240 fewer)		
New GAD lesions (number of patients free) (follow-up mean 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	65/171 (38%)	32/171 (18.7%)	RR 2.03 (1.41 to 2.93)	193 more per 1000 (from 77 more to 361 more)	⊕⊕⊕O MODERATE	CRITICAL
								18.7%		193 more per 1000 (from 77 more to 361 more)		
GAD lesions (mean number) (78 weeks' follow-up) (follow-up mean 78 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134	114	-	MD 1 lower (1.71 to 0.29 lower)	⊕⊕OO LOW	CRITICAL
New T2 lesions (number of patients free) (follow-up mean 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	120/171 (70.2%)	50/171 (29.2%)	RR 2.4 (1.86 to 3.09)	409 more per 1000 (from 251 more to 611 more)	⊕⊕⊕O MODERATE	CRITICAL
								29.2%		409 more per 1000 (from 251 more to 610 more)		
T2 new or newly enlarging lesions (mean number) (78 weeks' follow-up) (follow-up mean 78 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	132	119	-	MD 2.9 lower (4.39 to 1.41 lower)	⊕⊕OO LOW	CRITICAL
Change in T2 lesion volume (follow-up mean 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	292	176	-	MD 456.9 lower (959.46 lower to 45.66 higher)	⊕⊕⊕O MODERATE	CRITICAL
Cumulative number of newly active lesions (mean number) (follow-up mean 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	176	-	MD 4.8 lower (7.06 to 2.54 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Combined unique active lesions (mean number per patient per scan) (follow-up mean 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	171	171	-	MD 2.1 lower (2.9 to 1.3 lower)	⊕⊕⊕O MODERATE	CRITICAL
Discontinuation due to any reason (follow-up 104-156 weeks)												

3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	72/656 (11%)	57/537 (10.6%)	RR 1.11 (0.8 to 1.54)	12 more per 1000 (from 21 fewer to 57 more)	⊕⊕⊕O MODERATE	CRITICAL
								11.7%		13 more per 1000 (from 23 fewer to 63 more)		
Discontinuation due to side effects (follow-up 104-156 weeks)												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[2]	none	13/463 (2.8%)	6/347 (1.7%)	RR 2.17 (0.16 to 28.82)	20 more per 1000 (from 15 fewer to 481 more)	⊕⊕OO LOW	CRITICAL
								1.8%		21 more per 1000 (from 15 fewer to 501 more)		
Discontinuation of study drug due to side effects (follow-up 104-156 weeks)												
2	randomised trials	no serious risk of bias	very serious[5]	no serious indirectness	serious[2]	none	25/485 (5.2%)	8/366 (2.2%)	RR 0.98 (0.87 to 1.09)	0 fewer per 1000 (from 3 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
								2.1%		0 fewer per 1000 (from 3 fewer to 2 more)		
Discontinuation of study drug due to any reason (follow-up 104-156 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	82/485 (16.9%)	53/366 (14.5%)	RR 1.21 (0.88 to 1.67)	30 more per 1000 (from 17 fewer to 97 more)	⊕⊕⊕O MODERATE	CRITICAL
								14.3%		30 more per 1000 (from 17 fewer to 96 more)		
Mortality (risk of non-event) (follow-up 104-156 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/364 (0.27%)	2/361 (0.55%)	RR 1 (0.99 to 1.02)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.6%		0 fewer per 1000 (from 0 fewer to 0 more)		
Cognitive performance (PASAT-3") (follow-up mean 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	273	166	-	MD 1.4 higher (0.29 to 2.51 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Unclear allocation concealment and risk of selective outcome reporting (Jacobs 2000)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Confidence intervals include a null effect and appreciable benefit
[4] Substantial heterogeneity (I2=67%)
[5] Substantial and significant heterogeneity (I2=96%; p<0.00001)
[6] Confidence intervals include a negligible effect and appreciable benefit

2. Glatiramer acetate compared with placebo for clinically isolated syndrome

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glatiramer acetate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Time to conversion to CDMS (follow-up median 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	OR 0.55 (0.4 to 0.76)	-	□□□□ MODERATE	CRITICAL
								0%		-		
Discontinuation due to any reason (follow-up median 156 weeks)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	39/243 (16%)	23/238 (9.7%)	RR 1.66 (1.02 to 2.69)	64 more per 1000 (from 2 more to 163 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
								9.7%		64 more per 1000 (from 2 more to 164 more)		
Discontinuation due to side effects (follow-up median 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/243 (5.8%)	4/238 (1.7%)	RR 3.43 (1.14 to 10.26)	41 more per 1000 (from 2 more to 156 more)	⨁⨁◯◯ LOW	IMPORTANT
								1.7%		41 more per 1000 (from 2 more to 157 more)		

[1] Unclear risk of detection bias and unclear allocation concealment.

[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

3. Teriflunomide compared with placebo for clinically isolated syndrome

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriflunomide	Placebo	Relative (95% CI)	Absolute		
Time to conversion to CDMS (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/214 (17.8%)	55/197 (27.9%)	HR 0.57 (0.38 to 0.87)	109 fewer per 1000 (from 31 fewer to 162 fewer)	⊕⊕OO LOW	CRITICAL
								28.3%		110 fewer per 1000 (from 32 fewer to 164 fewer)		
Conversion to CDMS (number of participants) (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/214 (17.8%)	55/197 (27.9%)	RR 0.64 (0.44 to 0.92)	101 fewer per 1000 (from 22 fewer to 156 fewer)	⊕⊕OO LOW	CRITICAL
								28.3%		102 fewer per 1000 (from 23 fewer to 158 fewer)		
Disability progression (number of participants)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/214 (7.5%)	10/99 (10.1%)	RR 0.74 (0.35 to 1.57)	26 fewer per 1000 (from 66 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
								10.1%		26 fewer per 1000 (from 66 fewer to 58 more)		
Atrophy (mean change from baseline) (follow-up mean 108 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	99	68	-	MD 0 higher (0.01 lower to 0.01 higher)	⊕⊕OO LOW	CRITICAL
GAD lesions (mean number of lesions per MRI scan) (follow-up mean 108 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	74	110	-	MD 0.56 lower (1.17 lower to 0.06 higher)	⊕⊕OO LOW	CRITICAL
T2 lesion component (volume) (mean change from baseline) (follow-up mean 108 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	99	68	-	MD 0.07 lower (0.21 lower to 0.06 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation of study drug due to any reason (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/216 (23.6%)	56/197 (28.4%)	RR 0.83 (0.6 to 1.15)	48 fewer per 1000 (from 114 fewer to 43 more)	⊕⊕OO LOW	CRITICAL
								28.3%		48 fewer per 1000 (from 113 fewer to 42 more)		
Discontinuation of study drug due to side effects (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/216 (8.3%)	18/197 (9.1%)	RR 0.91 (0.49 to 1.7)	8 fewer per 1000 (from 47 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
								9.1%		8 fewer per 1000 (from 46 fewer to 64 more)		
Infection (number of participants) (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/216 (44.9%)	77/191 (39.3%)	RR 1.11 (0.89 to 1.4)	43 more per 1000 (from 43 fewer to 157 more)	⊕⊕OO	IMPORTANT

								39.4%		43 more per 1000 (from 43 fewer to 158 more)	LOW	
Serious infection (number of participants) (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/216 (3.2%)	1/191 (1%)	RR 3.09 (0.65 to 14.72)	22 more per 1000 (from 4 fewer to 144 more)	⊕⊕OO LOW	CRITICAL
								2%		42 more per 1000 (from 7 fewer to 274 more)		
Mortality (follow-up mean 108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/216 (0%)	1/197 (0.51%)	RR 1.01 (0.99 to 1.02)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
								1%		0 more per 1000 (from 0 fewer to 0 more)		

[1] High risk of bias due to incomplete outcome data
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Review question 2

1. Interferon compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	422/512 (82.4%)	358/500 (71.6%)	RR 1.15 (1.08 to 1.23)	107 more per 1000 (from 57 more to 165 more)	□□□□ MODERATE	CRITICAL
								71.6%		107 more per 1000 (from 57 more to 165 more)		
Relapse free (number of participants) (follow-up 104 weeks)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	178/573 (31.1%)	71/387 (18.3%)	RR 1.73 (1.35 to 2.21)	134 more per 1000 (from 64 more to 222 more)	□□□□ LOW	CRITICAL
								16%		117 more per 1000 (from 56 more to 194 more)		
Relapse free (number of participants) - 156 weeks FU (follow-up 156 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	27/124 (21.8%)	17/123 (13.8%)	RR 1.58 (0.91 to 2.74)	80 more per 1000 (from 12 fewer to 240 more)	□□□□ LOW	CRITICAL
								13.8%		80 more per 1000 (from 12 fewer to 240 more)		
Annualised relapse rate (follow-up 48-104 weeks; Better indicated by lower values)												
2	randomised	serious[5]	no serious	no serious	no serious	None	959	950	-	MD 0.1 lower (0.16 to 0.04	□□□□	CRITICAL

	trials		inconsistency	indirectness	imprecision					lower)	MODERATE	
Disability progression confirmed at 3 months (number of participants worsened) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/512 (6.1%)	50/500 (10%)	RR 0.61 (0.39 to 0.93)	39 fewer per 1000 (from 7 fewer to 61 fewer)	⨁◯◯◯ LOW	CRITICAL
								10%		39 fewer per 1000 (from 7 fewer to 61 fewer)		
Disability progression confirmed at 6 months (number of participants worsened) (follow-up 104 weeks)												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	53/532 (10%)	75/537 (14%)	RR 0.71 (0.51 to 0.98)	41 fewer per 1000 (from 3 fewer to 68 fewer)	⨁◯◯◯ LOW	CRITICAL
								21.8%		63 fewer per 1000 (from 4 fewer to 107 fewer)		
Disability progression (number of participants worsened) (follow-up 156 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	33/124 (26.6%)	48/123 (39%)	RR 0.68 (0.47 to 0.98)	125 fewer per 1000 (from 8 fewer to 207 fewer)	⨁◯◯◯ LOW	CRITICAL
								39%		125 fewer per 1000 (from 8 fewer to 207 fewer)		
Discontinuation due to side effects - 48 weeks FU (follow-up 48 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	24/512 (4.7%)	5/500 (1%)	RR 4.69 (1.8 to 12.19)	37 more per 1000 (from 8 more to 112 more)	⨁⨁◯◯ MODERATE	CRITICAL
								1%		37 more per 1000 (from 8 more to 112 more)		
Discontinuation due to any reason (follow-up 48 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	74/512 (14.5%)	44/500 (8.8%)	RR 1.64 (1.15 to 2.34)	56 more per 1000 (from 13 more to 118 more)	⨁⨁◯◯ MODERATE	CRITICAL
								8.8%		56 more per 1000 (from 13 more to 118 more)		
Discontinuation due to side effects (follow-up 104 weeks)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	48/905 (5.3%)	23/725 (3.2%)	RR 1.72 (1.04 to 2.86)	23 more per 1000 (from 1 more to 59 more)	⨁◯◯◯ LOW	CRITICAL
								1.7%		12 more per 1000 (from 1 more to 32 more)		
Discontinuation due to any reason (follow-up 104 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	110/820 (13.4%)	109/638 (17.1%)	RR 0.84 (0.65 to 1.07)	27 fewer per 1000 (from 60 fewer to 12 more)	⨁⨁◯◯ MODERATE	CRITICAL
								9.6%		15 fewer per 1000 (from 34 fewer to 7 more)		
Discontinuation due to side effects (follow-up 156 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	10/124 (8.1%)	2/123 (1.6%)	RR 4.96 (1.11 to 22.17)	64 more per 1000 (from 2 more to 344 more)	⨁◯◯◯ LOW	CRITICAL

								1.6%		63 more per 1000 (from 2 more to 339 more)		
Discontinuation due to any reason (follow-up 156 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	23/124 (18.5%)	24/123 (19.5%)	RR 0.95 (0.57 to 1.59)	10 fewer per 1000 (from 84 fewer to 115 more)	□□□□ LOW	CRITICAL
								19.5%		10 fewer per 1000 (from 84 fewer to 115 more)		
Lesion volume (mm3) (follow-up 156 weeks; Better indicated by lower values)												
1	randomised trials	serious[4,7]	no serious inconsistency	no serious indirectness	serious[3]	none	134	123	-	MD 26.5 lower (90.6 lower to 37.6 higher)	□□□□ LOW	CRITICAL
Lesion volume (mm3) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	82	82	-	MD 48.3 lower (169.42 lower to 72.82 higher)	□□□□ LOW	CRITICAL
New or newly enlarging T2 lesions (mean number) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	457	476	-	MD 7.3 lower (8.85 to 5.75 lower)	□□□□ MODERATE	CRITICAL
T2 active lesions (number of participants with no activity) (follow-up 104 weeks)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	91/367 (24.8%)	16/184 (8.7%)	RR 2.8 (1.69 to 4.63)	157 more per 1000 (from 60 more to 316 more)	□□□□ LOW	CRITICAL
								8.7%		157 more per 1000 (from 60 more to 316 more)		
Combined unique active lesions (number of participants with no activity) (follow-up 104 weeks)												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	48/132 (36.4%)	8/66 (12.1%)	RR 2.97 (1.49 to 5.92)	239 more per 1000 (from 59 more to 596 more)	□□□□ LOW	CRITICAL
								12.1%		238 more per 1000 (from 59 more to 595 more)		
Percent brain volume change (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	512	500	-	MD 0.1 lower (0.2 lower to 0 higher)	□□□□ MODERATE	CRITICAL
Percent brain volume change (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	447	450	-	MD 0.11 lower (0.28 lower to 0.06 higher)	□□□□ MODERATE	CRITICAL
Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	447	450	-	MD 1.44 lower (1.97 to 0.91 lower)	□□□□ MODERATE	CRITICAL
Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	447	450	-	MD 6.66 lower (9.04 to 4.28 lower)	□□□□ MODERATE	CRITICAL

[1] Unclear risk of detection bias

[2] Unclear risk of randomisation sequence generation (IFNB MS Group 1993). Unclear allocation concealment (IFNB MS Group 1993 and Jacobs 1996). Unclear risk of detection bias (IFNB MS Group 1993). Unclear risk of selective outcome reporting (all studies).

[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

[4] Method of randomisation sequence generation and allocation concealment unclear. Unclear risk of detection bias and selective outcome reporting.
[5] Unclear detection bias (Calabresi 2014). Unclear risk of performance bias - interferon was not blinded (Vollmer 2014)
[6] Unclear risk of performance bias (Vollmer 2014). Unclear risk of detection bias (Calabresi 2014)
[7] Unclear allocation concealment. Unclear risk of selective outcome reporting.
[8] Unclear risk of selective outcome reporting
[9] Unclear risk of performance bias

2. Glatiramer acetate compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glatiramer acetate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 52-104 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1006/1418 (70.9%)	550/950 (57.9%)	RR 1.17 (1.1 to 1.24)	98 more per 1000 (from 58 more to 139 more)	□□□□ MODERATE	CRITICAL
								59%		100 more per 1000 (from 59 more to 142 more)		
Annualised relapse rate (follow-up 52-96 weeks; Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1293	824	-	MD 0.14 lower (0.21 to 0.06 lower)	□□□□ MODERATE	CRITICAL
Disability progression (number of participants worsened) (follow-up 96-104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	82/475 (17.3%)	98/489 (20%)	RR 0.86 (0.66 to 1.11)	28 fewer per 1000 (from 68 fewer to 22 more)	□□□□ LOW	CRITICAL
								22.8%		32 fewer per 1000 (from 78 fewer to 25 more)		
Discontinuation due to any reason (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	84/943 (8.9%)	31/461 (6.7%)	RR 1.32 (0.89 to 1.97)	22 more per 1000 (from 7 fewer to 65 more)	□□□□ MODERATE	CRITICAL
								6.7%		21 more per 1000 (from 7 fewer to 65 more)		
Discontinuation due to any reason (follow-up 06-104 weeks)												
2	randomised trials					none	87/485 (17.9%)	102/489 (20.9%)	RR 0.86 (0.66 to 1.11)	29 fewer per 1000 (from 71 fewer to 23 more)		CRITICAL
								18.5%		26 fewer per 1000 (from 63 fewer to 20 more)		
Discontinuation due to side effects (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/360 (2.8%)	11/363 (3%)	RR 0.92 (0.39 to 2.13)	2 fewer per 1000 (from 18 fewer to 34 more)	□□□□ MODERATE	CRITICAL

								3%		2 fewer per 1000 (from 18 fewer to 34 more)		
Discontinuation due to side effects (follow-up 96-104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/1068 (3.2%)	7/587 (1.2%)	RR 2.63 (1.17 to 5.9)	19 more per 1000 (from 2 more to 58 more)	□□□□ LOW	CRITICAL
								1.1%		18 more per 1000 (from 2 more to 54 more)		
New or newly enlarged T2 lesions (mean number) (follow-up 96 weeks; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	153	139	-	MD 9.4 lower (14.26 to 4.54 lower)	□□□□ LOW	CRITICAL
GAD lesions (mean number) (follow-up 96 weeks; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	161	144	-	MD 1.3 lower (2.26 to 0.34 lower)	□□□□ LOW	CRITICAL
Relapse free (number of participants) (follow-up 128 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	42/125 (33.6%)	31/126 (24.6%)	RR 1.37 (0.92 to 2.02)	91 more per 1000 (from 20 fewer to 251 more)	□□□□ LOW	CRITICAL
								24.6%		91 more per 1000 (from 20 fewer to 251 more)		
Disability progression (number of participants worsened) (follow-up 128 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	29/125 (23.2%)	37/126 (29.4%)	RR 0.79 (0.52 to 1.2)	62 fewer per 1000 (from 141 fewer to 59 more)	□□□□ LOW	CRITICAL
								29.4%		62 fewer per 1000 (from 141 fewer to 59 more)		
Discontinuation due to any reason (follow-up 128 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	23/125 (18.4%)	29/126 (23%)	RR 0.8 (0.49 to 1.3)	46 fewer per 1000 (from 117 fewer to 69 more)	□□□□ LOW	CRITICAL
								23%		46 fewer per 1000 (from 117 fewer to 69 more)		
Cumulative gad-e T1 lesions at months 6 and 12 (mean) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	884	441	-	MD 0.73 lower (1.15 to 0.31 lower)	□□□□ HIGH	CRITICAL
Cumulative new or newly enlarging T2 lesions at months 6 and 12 (mean) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	884	441	-	MD 1.94 lower (3.03 to 0.85 lower)	□□□□ HIGH	CRITICAL
Percentage change in brain volume from baseline to month 12(mean) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	840	423	-	MD 0.07 lower (0.19 lower to 0.06 higher)	□□□□ HIGH	CRITICAL

[1] High risk of performance bias and attrition bias (different reasons for drop-out across groups) (Fox 2012). Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).
[2] High risk of performance bias and attrition bias (different reasons for drop-out across groups) (Fox 2012).
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).

3. Teriflunomide compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriflunomide	Placebo	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 48-108 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	484/728 (66.5%)	400/751 (53.3%)	RR 1.25 (1.16 to 1.36)	133 more per 1000 (from 85 more to 192 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								53%		132 more per 1000 (from 85 more to 191 more)		
Annualised relapse rate (follow-up 48-108 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	728	752	-	MD 0.18 lower (0.24 to 0.11 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Disability progression (number of participants worsened) (follow-up 104-108 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/728 (17.9%)	175/751 (23.3%)	RR 0.76 (0.62 to 0.93)	56 fewer per 1000 (from 16 fewer to 89 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								23.4%		56 fewer per 1000 (from 16 fewer to 89 fewer)		
Mortality (risk of non-event) (follow-up 48 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/372 (0.5%)	1/389 (0.3%)	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⨁◯◯◯ LOW	CRITICAL
								0.3%		0 fewer per 1000 (from 0 fewer to 0 more)		
Discontinuation due to side effects (follow-up 48-108 weeks)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[3]	none	96/730 (13.2%)	55/752 (7.3%)	RR 1.77 (1.02 to 3.07)	56 more per 1000 (from 1 more to 151 more)	⨁◯◯◯ VERY LOW	CRITICAL
								7.3%		56 more per 1000 (from 1 more to 151 more)		
Discontinuation due to any reason (follow-up 48-108 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	221/730 (30.3%)	229/752 (30.5%)	RR 1 (0.86 to 1.16)	0 fewer per 1000 (from 43 fewer to 49 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								30.4%		0 fewer per 1000 (from 43 fewer to 49 more)		
GAD lesions (estimated mean change) (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	363	-	MD 1.07 lower (1.4 to 0.74 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Total lesion volume (change from baseline) (Better indicated by lower values)												

1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	363	-	MD 1.49 lower (2.56 to 0.42 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Patients free from enhanced lesions (follow-up 108 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	230/359 (64.1%)	144/363 (39.7%)	RR 1.62 (1.39 to 1.87)	246 more per 1000 (from 155 more to 345 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								39.7%		246 more per 1000 (from 155 more to 345 more)		
Risk of not having cancer (number of participants with any neoplasm) (follow-up 48-108 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/730 (0.5%)	5/752 (0.7%)	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⨁◯◯◯ LOW	CRITICAL
								0.7%		0 fewer per 1000 (from 0 fewer to 0 more)		
Risk of infection (number of participants with any infection) (follow-up 48-108 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/730 (31%)	277/752 (36.8%)	RR 0.85 (0.75 to 0.98)	55 fewer per 1000 (from 7 fewer to 92 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								36.3%		54 fewer per 1000 (from 7 fewer to 91 fewer)		

[1] High risk of attrition bias (30% lost to follow-up with different reasons for drop out) (Confavreux 2014). Allocation concealment unclear (O'Conner 2011)
[2] High risk of attrition bias (30% lost to follow-up with different reasons for drop out)
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Substantial heterogeneity (I2=63%)
[5] Unclear allocation concealment

4. Dimethyl fumarate compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dimethyl fumarate	Placebo	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 104 weeks)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	554/769 (72%)	434/771 (56.3%)	RR 1.28 (1.14 to 1.43)	158 more per 1000 (from 79 more to 242 more)	□□□□ LOW	CRITICAL
								56.4%		158 more per 1000 (from 79 more to 243 more)		
Annualised relapse rate (follow-up 104 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	771	771	-	MD 0.19 lower (0.25 to 0.13 lower)	□□□□ MODERATE	CRITICAL
Disability progression (number of participants worsened) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	112/768 (14.6%)	172/771 (22.3%)	RR 0.66 (0.51 to 0.85)	76 fewer per 1000 (from 33 fewer to 109 fewer)	□□□□ LOW	CRITICAL
								22%		75 fewer per 1000 (from 33 fewer to 108 fewer)		
Discontinuation due to side effects (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	126/773 (16.3%)	130/773 (16.8%)	RR 0.97 (0.78 to 1.21)	5 fewer per 1000 (from 37 fewer to 35 more)	□□□□ LOW	CRITICAL
								16.7%		5 fewer per 1000 (from 37 fewer to 35 more)		
Mortality (follow-up 104 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	0/773 (0%)	1/773 (0.1%)	RR 1 (1 to 1)	-	□□□□ MODERATE	CRITICAL
								0.1%		-		
Discontinuation due to any reason (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	170/773 (22%)	176/773 (22.8%)	RR 0.97 (0.8 to 1.16)	7 fewer per 1000 (from 46 fewer to 36 more)	□□□□ LOW	CRITICAL
								22.8%		7 fewer per 1000 (from 46 fewer to 36 more)		
GAD lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	299	309	-	MD 1.64 lower (2.17 to 1.1 lower)	□□□□ MODERATE	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	304	-	MD 13.36 lower (16.63 to 10.09 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Risk of not having cancer (number of participants with any neoplasm) (follow-up 104 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/410 (0.5%)	2/408 (0.5%)	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⨁⨁◯◯ LOW	CRITICAL
								0.5%		0 fewer per 1000 (from 0 fewer to 0 more)		
Risk of serious infection (number of participants with any infection) (follow-up 104 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	10/410 (2.4%)	7/408 (1.7%)	RR 1.42 (0.55 to 3.7)	7 more per 1000 (from 8 fewer to 46 more)	⨁⨁◯◯ LOW	CRITICAL
								1.7%		7 more per 1000 (from 8 fewer to 46 more)		
Risk of infection (number of participants with any infection) (follow-up 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	88/359 (24.5%)	77/363 (21.2%)	RR 1.16 (0.88 to 1.51)	34 more per 1000 (from 25 fewer to 108 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								21.2%		34 more per 1000 (from 25 fewer to 108 more)		

[1] High risk of attrition bias (different reasons for loss to follow-up between groups). Allocation concealment unclear (Fox 2012).
[2] Substantial heterogeneity (I2=55%)
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[4] High risk of attrition bias (different reasons for loss to follow-up between groups).

5. Fingolimod compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fingolimod**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	555/783 (70.9%)	378/773 (48.9%)	RR 1.44 (1.28 to 1.63)	215 more per 1000 (from 137 more to 308 more)	□□□□ MODERATE	CRITICAL
								49.2%		216 more per 1000 (from 138 more to 310 more)		
Disability progression (number of participants worsened) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102/783 (13%)	142/773 (18.4%)	RR 0.71 (0.56 to 0.9)	53 fewer per 1000 (from 18 fewer to 81 fewer)	□□□□ LOW	CRITICAL
								18.3%		53 fewer per 1000 (from 18 fewer to 81 fewer)		
Annualised relapse rate (follow-up 104 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	783	855	-	MD 0.21 lower (0.25 to 0.16 lower)	□□□□ MODERATE	CRITICAL
GAD lesions (number of patients with no lesions) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	565/638 (88.6%)	383/588 (65.1%)	RR 1.36 (1.27 to 1.45)	234 more per 1000 (from 176 more to 293 more)	□□□□ MODERATE	CRITICAL
								65.2%		235 more per 1000 (from 176 more to 293 more)		
New or newly enlarged T2 lesions (number of patients with no lesions) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	320/634 (50.5%)	137/590 (23.2%)	RR 2.16 (1.77 to 2.63)	269 more per 1000 (from 179 more to 378 more)	□□□□ MODERATE	CRITICAL
								23.6%		274 more per 1000 (from 182 more to 385 more)		
Discontinuation due to any reason (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	142/783 (18.1%)	186/773 (24.1%)	RR 0.75 (0.57 to 0.99)	60 fewer per 1000 (from 2 fewer to 103 fewer)	□□□□ LOW	CRITICAL
								24.4%		61 fewer per 1000 (from 2 fewer to 105 fewer)		
Discontinuation due to side effects (follow-up 104 weeks)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	123/783 (15.7%)	86/773 (11.1%)	RR 1.42 (0.92 to 2.17)	47 more per 1000 (from 9 fewer to 130 more)	□□□□ VERY LOW	CRITICAL

								11.1%		47 more per 1000 (from 9 fewer to 130 more)		
GAD lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	638	578	-	MD 0.87 lower (1.1 to 0.64 lower)	□□□□ MODERATE	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	601	591	-	MD 7.03 lower (8.22 to 5.84 lower)	□□□□ MODERATE	CRITICAL
Change in brain volume (percent change) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	356	329	-	MD 0.3 higher (0.16 to 0.44 higher)	□□□□ MODERATE	CRITICAL
Risk of cancer (number of participants with any neoplasm) (follow-up 104 weeks)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[2]	none	17/783 (2.2%)	18/773 (2.3%)	RR 0.84 (0.21 to 3.34)	4 fewer per 1000 (from 18 fewer to 54 more)	□□□□ VERY LOW	CRITICAL
								2.3%		4 fewer per 1000 (from 18 fewer to 54 more)		
Risk of infection (number of participants with any infection) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	642/783 (82%)	612/773 (79.2%)	RR 1.04 (0.99 to 1.09)	32 more per 1000 (from 8 fewer to 71 more)	□□□□ MODERATE	CRITICAL
								78.6%		31 more per 1000 (from 8 fewer to 71 more)		

[1] High risk of attrition bias (differences in loss to follow-up between groups and different reasons for drop out). Unclear allocation concealment (Calabresi 2014b)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

6. Natalizumab compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Natalizumab**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	501/627 (79.9%)	189/315 (60%)	RR 1.33 (1.21 to 1.47)	198 more per 1000 (from 126 more to 282 more)	□□□□ HIGH	CRITICAL
								60%		198 more per 1000 (from 126 more to 282 more)		
Relapse free (number of participants) (follow-up 104 weeks)												
1	randomised	no serious risk	no serious	no serious	no serious	none	454/615	146/315	RR 1.59 (1.4 to	273 more per 1000 (from 185	□□□□	CRITICAL

	trials	of bias	inconsistency	indirectness	imprecision		(73.8%)	(46.3%)	1.81)	more to 375 more)	HIGH	
								46.4%		274 more per 1000 (from 186 more to 376 more)		
Cumulative disability progression (number of participants worsened) (follow-up 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	106/627 (16.9%)	91/315 (28.9%)	RR 0.59 (0.46 to 0.75)	118 fewer per 1000 (from 72 fewer to 156 fewer)	□□□□ MODERATE	CRITICAL
								28.9%		118 fewer per 1000 (from 72 fewer to 156 fewer)		
Annualised relapse rate (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	MD 0.51 lower (0.67 to 0.35 lower)	□□□□ HIGH	CRITICAL
Annualised relapse rate (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	MD 0.5 lower (0.63 to 0.37 lower)	□□□□ HIGH	CRITICAL
Discontinuation due to side effects (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15/627 (2.4%)	6/315 (1.9%)	RR 1.26 (0.49 to 3.21)	5 more per 1000 (from 10 fewer to 42 more)	□□□□ MODERATE	CRITICAL
								1.9%		5 more per 1000 (from 10 fewer to 42 more)		
Discontinuation due to any reason (follow-up 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	52/627 (8.3%)	31/315 (9.8%)	RR 0.84 (0.55 to 1.29)	16 fewer per 1000 (from 44 fewer to 29 more)	□□□□ MODERATE	CRITICAL
								9.8%		16 fewer per 1000 (from 44 fewer to 28 more)		
GAD lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	SMD 0.56 lower (0.7 to 0.42 lower)	□□□□ HIGH	CRITICAL
GAD lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	SMD 0.43 lower (0.57 to 0.3 lower)	□□□□ HIGH	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	MD 4.9 lower (5.96 to 3.84 lower)	□□□□ HIGH	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	MD 9.1 lower (10.98 to 7.22 lower)	□□□□ HIGH	CRITICAL
Risk of cancer (risk of non-event; number of participants with any neoplasm) (follow-up 104 weeks)												
1	randomised	no serious risk	no serious	no serious	serious[1]	none	5/627	1/315	RR 1 (0.99 to	0 fewer per 1000 (from 0	□□□□	CRITICAL

	trials	of bias	inconsistency	indirectness			(0.8%)	(0.3%)	1)	fewer to 0 more)	MODERATE	
								0.3%		0 fewer per 1000 (from 0 fewer to 0 more)		
Risk of infection (number of participants with any infection) (follow-up 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	527/627 (84.1%)	215/315 (68.3%)	RR 1.23 (1.13 to 1.34)	157 more per 1000 (from 89 more to 232 more)	□□□□ HIGH	CRITICAL
								68.3%		157 more per 1000 (from 89 more to 232 more)		
Mortality (risk of non-event)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/627 (0.3%)	0/315 (0%)	RR 1 (0.99 to 1)	-	□□□□ MODERATE	CRITICAL
								0%		-		

1 Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7. Daclizumab compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daclizumab	Placebo	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	163/201 (81.1%)	127/196 (64.8%)	RR 1.25 (1.11 to 1.42)	162 more per 1000 (from 71 more to 272 more)	□□□□ MODERATE	CRITICAL
								64.8%		162 more per 1000 (from 71 more to 272 more)		
Disability progression (number of participants worsened) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/201 (5.5%)	25/196 (12.8%)	RR 0.43 (0.22 to 0.85)	73 fewer per 1000 (from 19 fewer to 99 fewer)	□□□□ LOW	CRITICAL
								12.8%		73 fewer per 1000 (from 19 fewer to 100 fewer)		
Annualised relapse rate (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	201	196	-	MD 0.25 lower (0.37 to 0.13 lower)	□□□□ HIGH	CRITICAL
Discontinuation due to any reason												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19/201 (9.5%)	18/196 (9.2%)	RR 1.03 (0.56 to 1.9)	3 more per 1000 (from 40 fewer to 83 more)	□□□□ MODERATE	CRITICAL
								9.2%		3 more per 1000 (from 40 fewer to 83 more)		
Discontinuation due to side effects (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/201 (3%)	2/196 (1%)	RR 2.93 (0.6 to 14.32)	20 more per 1000 (from 4 fewer to 136 more)	□□□□ MODERATE	CRITICAL
								1%		19 more per 1000 (from 4 fewer to 133 more)		
Brain atrophy (% change in whole brain volume) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	198	196	-	MD 0.05 lower (0.22 lower to 0.12 higher)	□□□□ LOW	CRITICAL
GAD lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199	195	-	MD 1.1 lower (1.45 to 0.75 lower)	□□□□ MODERATE	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	199	195	-	MD 5.7 lower (7.38 to 4.02 lower)	□□□□ MODERATE	CRITICAL
Risk of malignancy (risk of non-event; number of participants with any neoplasm) (follow-up 52 weeks)												
1	randomised	no serious risk	no serious	no serious	serious[2]	none	1/208	1/204	RR 1 (0.99 to	0 fewer per 1000 (from 0	□□□□	CRITICAL

	trials	of bias	inconsistency	indirectness			(0.5%)	(0.5%)	1.01)	fewer to 0 more)	MODERATE	
								0.5%		0 fewer per 1000 (from 0 fewer to 0 more)		
Risk of infection (number of participants with any infection) (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	104/208 (50%)	89/204 (43.6%)	RR 1.15 (0.93 to 1.41)	65 more per 1000 (from 31 fewer to 179 more)	□□□□ MODERATE	CRITICAL
								43.6%		65 more per 1000 (from 31 fewer to 179 more)		
Mortality (risk of non-event) (follow-up 52 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/201 (0.5%)	0/196 (0%)	RR 1 (0.98 to 1.01)	-	□□□□ MODERATE	CRITICAL
								0%		-		

[1] High risk of reporting bias for secondary outcomes (Quality of life reported but not specified in protocol)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] 95% confidence interval around the pooled estimate of effect includes no effect and appreciable

8. Cladribine compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cladribine	Placebo	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	705/889 (79.3%)	266/438 (60.7%)	RR 1.31 (1.2 to 1.42)	188 more per 1000 (from 121 more to 255 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								60.7%		188 more per 1000 (from 121 more to 255 more)		
Annualised relapse rate (follow-up 96 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	889	438	-	MD 0.19 lower (0.23 to 0.14 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation due to any reason (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	85/889 (9.6%)	58/438 (13.2%)	RR 0.72 (0.53 to 0.99)	37 fewer per 1000 (from 1 fewer to 62 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								13.2%		37 fewer per 1000 (from 1 fewer to 62 fewer)		
Discontinuation due to side effects (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	14/889 (1.6%)	6/438 (1.4%)	RR 1.13 (0.43 to 2.94)	2 more per 1000 (from 8 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
								1.4%		2 more per 1000 (from 8 fewer to 27 more)		
Risk of any infection (number of participants with any infection) (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	427/884 (48.3%)	186/436 (42.7%)	RR 1.13 (1 to 1.29)	55 more per 1000 (from 0 more to 124 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								42.7%		56 more per 1000 (from 0 more to 124 more)		
Risk of serious infection (number of participants with any infection) (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	23/884 (2.6%)	8/436 (1.8%)	RR 1.41 (0.64 to 3.13)	8 more per 1000 (from 7 fewer to 39 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.8%		7 more per 1000 (from 6 fewer to 38 more)		
Risk of cancer (number of participants with any neoplasm) (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/884 (1.1%)	0/436 (0%)	RR 5.37 (0.69 to 41.55)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Mortality(number of participants with any infection) (follow-up 96 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	4/889 (0.4%)	2/438 (0.5%)	RR 0.99 (0.18 to 5.36)	0 fewer per 1000 (from 4 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
								0.5%		0 fewer per 1000 (from 4 fewer		

										to 22 more)		

[1] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2] Confidence intervals include a negligible effect and appreciable benefit

9. Interferon compared with glatiramer acetate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon**	**Glatiramer acetate**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 96-104 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	773/1310 (59%)	526/865 (60.8%)	RR 0.98 (0.9 to 1.06)	12 fewer per 1000 (from 61 fewer to 36 more)	□□□□ MODERATE	CRITICAL
								61.9%		12 fewer per 1000 (from 62 fewer to 37 more)		
Annualised relapse rate (follow-up 96-104 weeks; Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	93	56	-	MD 0.05 lower (0.21 lower to 0.11 higher)		CRITICAL
Disability progression (number of participants worsened) (follow-up 104 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	186/888 (20.9%)	90/448 (20.1%)	RR 1.04 (0.83 to 1.31)	8 more per 1000 (from 34 fewer to 62 more)	□□□□ MODERATE	CRITICAL
								20.1%		8 more per 1000 (from 34 fewer to 62 more)		
GAD lesions (number of patients with no lesions) (follow-up 06 weeks)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	186/230 (80.9%)	154/230 (67%)	RR 1.21 (1.08 to 1.35)	141 more per 1000 (from 54 more to 234 more)	□□□□ LOW	CRITICAL
								67%		141 more per 1000 (from 54 more to 235 more)		
New or newly enlarged T2 lesions (number of patients with no lesions)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	93/230 (40.4%)	86/230 (37.4%)	RR 1.08 (0.86 to 1.36)	30 more per 1000 (from 52 fewer to 135 more)	□□□□ LOW	
								37.4%		30 more per 1000 (from 52 fewer to 135 more)		
New T2 white matter lesion (mean number) (follow-up 104 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	93	56	-	MD 0.05 higher (0.29 lower to 0.39 higher)	□□□□ LOW	CRITICAL
New GAD lesions (mean number) (follow-up 104 weeks; Better indicated by lower values)												

1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	93	56	-	MD 0.15 lower (0.48 lower to 0.17 higher)	⨁◯◯◯ LOW	CRITICAL
Combined active lesions (number of participants free from) (follow-up 104 weeks)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	10/36 (27.8%)	12/39 (30.8%)	RR 0.9 (0.45 to 1.83)	31 fewer per 1000 (from 169 fewer to 255 more)	⨁◯◯◯ LOW	CRITICAL
								30.8%		31 fewer per 1000 (from 169 fewer to 256 more)		
New lesions (number of participants free from) (follow-up 104 weeks)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	17/36 (47.2%)	18/39 (46.2%)	RR 1.02 (0.63 to 1.66)	9 more per 1000 (from 171 fewer to 305 more)	⨁◯◯◯ LOW	CRITICAL
								46.2%		9 more per 1000 (from 171 fewer to 305 more)		
New cortical lesions (mean number) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	86	44	-	MD 0.36 lower (1.24 lower to 0.52 higher)	⨁◯◯◯ LOW	CRITICAL
Discontinuation due to any reason (follow-up 208 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	24/110 (21.8%)	12/56 (21.4%)	RR 1.02 (0.55 to 1.88)	4 more per 1000 (from 96 fewer to 189 more)	⨁◯◯◯ LOW	CRITICAL
								21.4%		4 more per 1000 (from 96 fewer to 188 more)		
Discontinuation due to side effects (follow-up 208 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	14/110 (12.7%)	4/56 (7.1%)	RR 1.78 (0.62 to 5.16)	56 more per 1000 (from 27 fewer to 297 more)	⨁◯◯◯ LOW	CRITICAL
								7.1%		55 more per 1000 (from 27 fewer to 295 more)		
Discontinuation due to side effects (follow-up 48-104 weeks)												
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	51/1420 (3.6%)	33/921 (3.6%)	RR 1.15 (0.75 to 1.77)	5 more per 1000 (from 9 fewer to 28 more)	⨁◯◯◯ LOW	CRITICAL
								5.1%		8 more per 1000 (from 13 fewer to 39 more)		
Discontinuation due to any reason (follow-up 48-104 weeks)												
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	147/1420 (10.4%)	89/921 (9.7%)	RR 1.3 (0.68 to 2.47)	29 more per 1000 (from 31 fewer to 142 more)	⨁◯◯◯ LOW	CRITICAL
								14.3%		43 more per 1000 (from 46 fewer to 210 more)		
Mortality (risk of non-event) (follow-up 104 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	0/888 (0%)	1/448 (0.2%)	RR 1 (1 to 1.01)	0 fewer per 1000 (from 0 more to 0 more)	⨁◯◯◯ LOW	CRITICAL
								0.2%		0 fewer per 1000 (from 0 more to 0 more)		

[1] Unclear allocation concealment (all studies). High risk of performance bias (Mikol 2008). Unclear risk of performance bias (O'Conner 2009). High risk of missing outcome data (O'Conner 2009).
[2] Unclear risk of perfonmance bias. Unclear allocation concealment. High risk of missing outcome data.

[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Unclear allocation concealment. Unclear risk of performance bias. High risk of missing outcome data.
[5] High risk of performance bias.
[6] Unclear allocation concealment
[7] Unclear allocation concealment (all studies). High risk of performance bias (Mikol 2008). Unclear risk of performance bias (O'Conner 2009). High risk of missing outcome data (O'Conner 2009). Unclear detection bias (Calabrese 2012).

10. Teriflunomide compared with interferon

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Teriflunomide**	**Interferon**	**Relative (95% CI)**	**Absolute**		
Relapse free (number of participants) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	63/109 (57.8%)	88/104 (84.6%)	RR 0.68 (0.57 to 0.82)	271 fewer per 1000 (from 152 fewer to 364 fewer)	□□□□ LOW	CRITICAL
								84.6%		271 fewer per 1000 (from 152 fewer to 364 fewer)		
Annualised relapse rate (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	111	104	-	MD 0.04 higher (0.17 lower to 0.25 higher)	□□□□ LOW	CRITICAL
Discontinuation due to side effects (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/111 (10.8%)	22/104 (21.2%)	RR 0.51 (0.27 to 0.98)	104 fewer per 1000 (from 4 fewer to 154 fewer)	□□□□ LOW	CRITICAL
								21.2%		104 fewer per 1000 (from 4 fewer to 155 fewer)		
Discontinuation due to any reason (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/111 (19.8%)	30/104 (28.8%)	RR 0.69 (0.42 to 1.11)	89 fewer per 1000 (from 167 fewer to 32 more)	□□□□ LOW	CRITICAL
								28.9%		90 fewer per 1000 (from 168 fewer to 32 more)		
Risk of infection (number of participants with any infection) (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/111 (48.6%)	47/104 (45.2%)	RR 1.08 (0.81 to 1.43)	36 more per 1000 (from 86 fewer to 194 more)	□□□□ LOW	CRITICAL
								45.2%		36 more per 1000 (from 86 fewer to 194 more)		

[1] High risk of performance bias (interferon was open-label) and high risk of attrition bias (differential loss to follow-up between groups). Allocation concealment was not reported (unclear selection bias).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

11. Fingolimod compared with interferon

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fingolimod	Interferon	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354/429 (82.5%)	298/431 (69.1%)	RR 1.19 (1.11 to 1.29)	131 more per 1000 (from 76 more to 201 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								69.1%		131 more per 1000 (from 76 more to 200 more)		
Disability progression (number of participants worsened) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/429 (5.8%)	34/431 (7.9%)	RR 0.74 (0.45 to 1.22)	21 fewer per 1000 (from 43 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
								7.9%		21 fewer per 1000 (from 43 fewer to 17 more)		
Annualised relapse rate (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	429	431	-	MD 0.17 lower (0.26 to 0.08 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
GAD lesions (number of patients with no lesions) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	337/374 (90.1%)	286/354 (80.8%)	RR 1.12 (1.05 to 1.19)	97 more per 1000 (from 40 more to 154 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								80.8%		97 more per 1000 (from 40 more to 154 more)		
New or newly enlarged T2 lesions (number of patients with no lesions) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	204/372 (54.8%)	165/361 (45.7%)	RR 1.2 (1.04 to 1.39)	91 more per 1000 (from 18 more to 178 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								45.7%		91 more per 1000 (from 18 more to 178 more)		
Discontinuation due to side effects (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/429 (10.5%)	32/431 (7.4%)	RR 1.41 (0.92 to 2.18)	30 more per 1000 (from 6 fewer to 88 more)	⨁⨁◯◯ LOW	CRITICAL
								7.4%		30 more per 1000 (from 6 fewer to 87 more)		
Discontinuation due to any reason (follow-up 52 weeks)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	31/429	45/431	RR 0.69 (0.45	32 fewer per 1000 (from 57	⨁⨁◯◯	CRITICAL

	trials		inconsistency	indirectness			(7.2%)	(10.4%)	to 1.07)	fewer to 7 more)	LOW	
								10.4%		32 fewer per 1000 (from 57 fewer to 7 more)		
GAD lesions (mean number) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	374	354	-	MD 0.28 lower (0.5 to 0.06 lower)	⨁⨁⨁◯ LOW	CRITICAL
New or newly enlarged T2 lesions (mean number) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	372	361	-	MD 0.9 lower (1.62 to 0.18 lower)	⨁⨁⨁◯ LOW	CRITICAL
Risk of not having cancer (number of participants with any neoplasm) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/429 (0%)	0/431 (0%)	RR 1 (1 to 1)	-	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		
Risk of infection (number of participants with any infection) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	184/429 (42.9%)	184/431 (42.7%)	RR 1 (0.86 to 1.17)	0 fewer per 1000 (from 60 fewer to 73 more)	⨁⨁⨁◯ LOW	CRITICAL
								42.7%		0 fewer per 1000 (from 60 fewer to 73 more)		

[1] Unclear risk of detection bias (unclear if rater blinded to participant treatment group). High risk of selective outcome reporting (MSCF measure not listed on protocol but reported in paper).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Confidence intervals include a negligible effect and appreciable benefit

12. Daclizumab compared with interferon

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daclizumab	Interferon	Relative (95% CI)	Absolute		
Relapse free (number of participants) (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	616/919 (67%)	470/922 (51%)	RR 1.31 (1.22 to 1.42)	158 more per 1000 (from 112 more to 214 more)	□□□□ MODERATE	CRITICAL
								51%		158 more per 1000 (from 112 more to 214 more)		
Disability progression (number of participants worsened) (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/919 (16%)	184/922 (20%)	RR 0.8 (0.66 to 0.98)	40 fewer per 1000 (from 4 fewer to 68 fewer)	□□□□ MODERATE	CRITICAL
								20%		40 fewer per 1000 (from 4 fewer to 68 fewer)		
Annualised relapse rate (follow-up 144 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	919	922	-	MD 0.17 lower (0.22 to 0.12 lower)	□□□□ MODERATE	CRITICAL
Discontinuation due to side effects (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56/919 (6.1%)	47/922 (5.1%)	RR 1.2 (0.82 to 1.74)	10 more per 1000 (from 9 fewer to 38 more)	□□□□ LOW	CRITICAL
								5.1%		10 more per 1000 (from 9 fewer to 38 more)		
Discontinuation due to any reason (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	195/919 (21.2%)	228/922 (24.7%)	RR 0.86 (0.73 to 1.01)	35 fewer per 1000 (from 67 fewer to 2 more)	□□□□ MODERATE	CRITICAL
								24.7%		35 fewer per 1000 (from 67 fewer to 2 more)		
New or newly enlarged T2 lesions (mean number) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	864	841	-	MD 5.20 lower (6.3 to 4.1 lower)	□□□□ MODERATE	CRITICAL
Risk of cancer (risk of non-event; number of participants with any neoplasm) (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	7/919 (0.8%)	8/922 (0.9%)	RR 0.88 (0.32 to 2.41)	1 fewer per 1000 (from 6 fewer to 12 more)	□□□□ LOW	CRITICAL
								0.9%		1 fewer per 1000 (from 6 fewer to 13 more)		
Risk of infection (number of participants with any infection) (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	595/919 (64.7%)	523/922 (56.7%)	RR 1.14 (1.06 to 1.23)	79 more per 1000 (from 34 more to 130 more)	□□□□ MODERATE	CRITICAL

								56.7%		79 more per 1000 (from 34 more to 130 more)		
Mortality (risk of non-event) (follow-up 144 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/919 (0.1%)	4/922 (0.4%)	RR 1 (1 to 1.01)	0 fewer per 1000 (from 0 more to 0 more)	□□□□ LOW	CRITICAL
								0.4%		0 fewer per 1000 (from 0 more to 0 more)		

[1] High risk of attrition bias (30% loss to follow-up). Unclear detection bias
[2] 95% confidence interval around the pooled estimate of effect includes no effect and appreciable benefit
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

13. Alemtuzumab compared with interferon

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alemtuzumab	Interferon	Relative (95% CI)	Absolute		
Relapse free (number of participants relapse free) (follow-up 104-156 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	657/914 (71.9%)	261/500 (52.2%)	RR 1.38 (1.26 to 1.51)	198 more per 1000 (from 136 more to 266 more)	□□□□ MODERATE	CRITICAL
								51.4%		195 more per 1000 (from 134 more to 262 more)		
Relapse free (number of participants relapse free) (follow-up 260 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	76/112 (67.9%)	45/111 (40.5%)	RR 1.67 (1.29 to 2.17)	272 more per 1000 (from 118 more to 474 more)	□□□□ LOW	CRITICAL
								40.5%		271 more per 1000 (from 117 more to 474 more)		
Annualised relapse rate (follow-up 104-156 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	538	313	-	MD 0.25 lower (0.33 to 0.18 lower)	□□□□ MODERATE	CRITICAL
Annualised relapse rate (follow-up 260 weeks; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	112	111	-	MD 0.23 lower (0.3 to 0.16 lower)	□□□□ LOW	CRITICAL
Disability progression (number of participants worsened) (follow-up 104-156 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	92/914 (10.1%)	84/500 (16.8%)	RR 0.59 (0.4 to 0.86)	69 fewer per 1000 (from 24 fewer to 101 fewer)	□□□□ LOW	CRITICAL
								19.8%		81 fewer per 1000 (from 28 fewer to 119 fewer)		
Disability progression (number of participants worsened) (follow-up 260 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	13/112 (11.6%)	30/111 (27%)	RR 0.43 (0.24 to 0.78)	154 fewer per 1000 (from 59 fewer to 205 fewer)	□□□□ LOW	CRITICAL
								27%		154 fewer per 1000 (from 59 fewer to 205 fewer)		
T2 Lesions (number of participants) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	362/779 (46.5%)	226/374 (60.4%)	RR 0.77 (0.6 to 1)	139 fewer per 1000 (from 242 fewer to 0 more)	□□□□ MODERATE	CRITICAL
								60.4%		139 fewer per 1000 (from 242 fewer to 0 more)		
Discontinuation due to side effects (follow-up 104-156 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	21/919 (2.3%)	39/496 (7.9%)	RR 0.31 (0.17 to 0.55)	54 fewer per 1000 (from 35 fewer to 65 fewer)	□□□□ LOW	CRITICAL
								7.4%		51 fewer per 1000 (from 33 fewer to 61 fewer)		

Discontinuation due to side effects (follow-up 260 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/108 (4.6%)	14/107 (13.1%)	RR 0.35 (0.13 to 0.95)	85 fewer per 1000 (from 7 fewer to 114 fewer)	⨁◯◯◯ LOW	CRITICAL
								13.1%		85 fewer per 1000 (from 7 fewer to 114 fewer)		
Discontinuation due to any reason (follow-up 104-156 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	83/935 (8.9%)	149/537 (27.7%)	RR 0.36 (0.25 to 0.52)	178 fewer per 1000 (from 133 fewer to 208 fewer)	⨁◯◯◯ LOW	CRITICAL
								31.6%		202 fewer per 1000 (from 152 fewer to 237 fewer)		
Infection (number of participants with any infection) (follow-up 104-156 weeks)												
3	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	658/919 (71.6%)	269/496 (54.2%)	RR 1.32 (1.1 to 1.58)	174 more per 1000 (from 54 more to 315 more)	⨁◯◯◯ LOW	CRITICAL
								46.7%		149 more per 1000 (from 47 more to 271 more)		
Infection (number of participants with any infection) (follow-up 260 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	77/108 (71.3%)	54/107 (50.5%)	RR 1.41 (1.13 to 1.76)	207 more per 1000 (from 66 more to 384 more)	⨁◯◯◯ LOW	CRITICAL
								50.5%		207 more per 1000 (from 66 more to 384 more)		
Mortality (risk of non-event) (follow-up 104-156 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	4/919 (0.4%)	0/496 (0%)	RR 1 (0.99 to 1)	-	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Mortality (follow-up 260 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	1/108 (0.9%)	1/107 (0.9%)	RR 1 (0.97 to 1.03)	0 fewer per 1000 (from 0 fewer to 0 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0.9%		0 fewer per 1000 (from 0 fewer to 0 more)		
Autoimmune disorders (number of participants with any disorder) (104-156 weeks' follow-up) (follow-up 104-156 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	8/919 (0.9%)	1/496 (0.2%)	RR 2.68 (0.56 to 12.9)	3 more per 1000 (from 1 fewer to 24 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Autoimmune disorders (number of participants with any disorder) (follow-up 260 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	2/108 (1.9%)	1/107 (0.9%)	RR 1.98 (0.18 to 21.53)	9 more per 1000 (from 8 fewer to 192 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0.9%		9 more per 1000 (from 7 fewer to 185 more)		
Malignancy (number of participants with any) (follow-up 260 weeks)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	4/919 (0.4%)	3/496 (0.6%)	See comment	0 more per 1000 (from 10 fewer to 10 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0.9%		0 more per 1000 (from 15		

										fewer to 15 more)		

[1] High risk or performance bias (all studies were open label). High risk of detection bias in Coles 2012 and Cohen 2012 - "In the absence of a masked rater, unmasked raters could submit EDSS assessments"
[2] High risk of performance bias (open-label)
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Substantial and significant heterogeneity (I2=71%; p=0.03)

14. Ocrelizumab compared with interferon

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ocrelizumab**	**Interferon**	**Relative (95% CI)**	**Absolute**		
Disability improvement (confirmed at 12 weeks) (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	130/628 (20.7%)	96/614 (15.6%)	RR 1.32 (1.04 to 1.68)	50 more per 1000 (from 6 more to 106 more)	□□□□ LOW	CRITICAL
								15.6%		50 more per 1000 (from 6 more to 106 more)		
Disability improvement (confirmed at 24 weeks) (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98/628 (15.6%)	71/614 (11.6%)	RR 1.35 (1.02 to 1.79)	40 more per 1000 (from 2 more to 91 more)	□□□□ LOW	CRITICAL
								11.6%		41 more per 1000 (from 2 more to 92 more)		
Disability progression (follow-up 96 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73/724 (10.1%)	109/655 (16.6%)	RR 0.6 (0.46 to 0.8)	67 fewer per 1000 (from 33 fewer to 90 fewer)	□□□□ LOW	CRITICAL
								16.7%		67 fewer per 1000 (from 33 fewer to 90 fewer)		
Infections and infestations (number of participants) (follow-up 096 weeks)												
1	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	482/825 (58.4%)	433/826 (52.4%)	RR 1.11 (1.02 to 1.22)	58 more per 1000 (from 10 more to 115 more)	□□□□ MODERATE	CRITICAL
								52.4%		58 more per 1000 (from 10 more to 115 more)		
One or more serious adverse event (number of participants) (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	57/825 (6.9%)	72/826 (8.7%)	RR 0.79 (0.57 to 1.11)	18 fewer per 1000 (from 37 fewer to 10 more)	□□□□ LOW	CRITICAL
								8.7%		18 fewer per 1000 (from 37 fewer to 10 more)		
Influenza-like illness (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	38/825 (4.6%)	177/826 (21.4%)	RR 0.21 (0.15 to 0.3)	169 fewer per 1000 (from 150 fewer to 182 fewer)	□□□□ MODERATE	CRITICAL

								21.4%		169 fewer per 1000 (from 150 fewer to 182 fewer)		
Mortality (risk of non-event) (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	1/825 (0.1%)	2/826 (0.2%)	RR 1 (1 to 1.01)	0 fewer per 1000 (from 0 more to 0 more)	□□□□ MODERATE	CRITICAL
								0.2%		0 fewer per 1000 (from 0 more to 0 more)		
Malignancies (risk of non-event) (follow-up 96 weeks)												
1	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	4/825 (0.5%)	2/826 (0.2%)	RR 1 (0.99 to 1)	0 fewer per 1000 (from 0 fewer to 0 more)	□□□□ MODERATE	CRITICAL
								0.2%		0 fewer per 1000 (from 0 fewer to 0 more)		
Discontinuation due to adverse events (follow-up 96 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/827 (3.5%)	64/829 (7.7%)	RR 0.46 (0.3 to 0.7)	42 fewer per 1000 (from 23 fewer to 54 fewer)	□□□□ LOW	CRITICAL
								7.7%		42 fewer per 1000 (from 23 fewer to 54 fewer)		
Discontinuation due to any reason (follow-up 96 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	99/827 (12%)	166/829 (20%)	RR 0.6 (0.48 to 0.75)	80 fewer per 1000 (from 50 fewer to 104 fewer)	□□□□ LOW	CRITICAL
								20%		80 fewer per 1000 (from 50 fewer to 104 fewer)		

[1] Unclear risk of selection bias, attrition bias, detection bias and selective outcome reporting (full report not available).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Unclear risk - studies combined

15. Interferon compared with placebo for secondary progressive multiple sclerosis

Quality assessment						No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Interferon**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression sustained at 3 months (follow-up 156 weeks)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	140/360 (38.9%)	178/358 (49.7%)	RR 0.78 (0.66 to 0.92)	109 fewer per 1000 (from 40 fewer to 169 fewer)	□□□□ MODERATE	CRITICAL
							49.7%		109 fewer per 1000 (from 40 fewer to 169 fewer)		

Disability progression sustained at 6 months (follow-up 156 weeks)											
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	325/863 (37.7%)	347/844 (41.1%)	RR 0.92 (0.8 to 1.06)	33 fewer per 1000 (from 82 fewer to 25 more)	□□□□ MODERATE	CRITICAL
							38.2%		31 fewer per 1000 (from 76 fewer to 23 more)		
Number of participants wheelchair bound (follow-up 156 weeks)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	60/360 (16.7%)	88/358 (24.6%)	RR 0.68 (0.51 to 0.91)	79 fewer per 1000 (from 22 fewer to 120 fewer)	□□□□ MODERATE	CRITICAL
							24.6%		79 fewer per 1000 (from 22 fewer to 121 fewer)		
Relapse (number of participants free from) (follow-up 156 weeks)											
2	randomised trials	serious[2]	serious	no serious indirectness	no serious imprecision	340/503 (67.6%)	302/486 (62.1%)	RR 1.08 (0.94 to 1.24)	50 more per 1000 (from 37 fewer to 149 more)	□□□□ LOW	CRITICAL
							62.1%		50 more per 1000 (from 37 fewer to 149 more)		
Discontinuation due to any reason (follow-up 156 weeks)											
4	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	136/1276 (10.7%)	108/1050 (10.3%)	RR 1.05 (0.77 to 1.42)	5 more per 1000 (from 24 fewer to 43 more)	□□□□ LOW	CRITICAL
							9.7%		5 more per 1000 (from 22 fewer to 41 more)		
Discontinuation due to side effects (follow-up 156 weeks)											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	49/599 (8.2%)	12/384 (3.1%)	RR 2.65 (1.42 to 4.95)	52 more per 1000 (from 13 more to 123 more)	□□□□ LOW	CRITICAL
							2.9%		48 more per 1000 (from 12 more to 115 more)		
Discontinuation of study drug due to any reason (follow-up 156 weeks)											
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	181/863 (21%)	166/844 (19.7%)	RR 1.07 (0.87 to 1.3)	14 more per 1000 (from 26 fewer to 59 more)	□□□□ MODERATE	CRITICAL
							18.4%		13 more per 1000 (from 24 fewer to 55 more)		
Discontinuation of study drug due to side effects (follow-up 156 weeks)											
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	75/677 (11.1%)	27/666 (4.1%)	RR 2.73 (1.78 to 4.19)	70 more per 1000 (from 32 more to 129 more)	□□□□ LOW	CRITICAL
							4%		69 more per 1000 (from 31 more to 128 more)		
Mortality (follow-up 156 weeks)											
4	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	12/1276 (0.9%)	6/1050 (0.6%)	RR 1.5 (0.55 to 4.13)	3 more per 1000 (from 3 fewer to 18 more)	□□□□ LOW	CRITICAL
							1%		5 more per 1000 (from 4 fewer to 31 more)		

Number of participants free from new or newly enlarging T2 lesion (follow-up 156 weeks)											
2	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	156/404 (38.6%)	48/200 (24%)	RR 1.61 (1.22 to 2.12)	146 more per 1000 (from 53 more to 269 more)	□□□□ LOW	CRITICAL
							24%		146 more per 1000 (from 53 more to 269 more)		
Combined unique activity (number of participants free) (follow-up 156 weeks)											
3	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	188/531 (35.4%)	80/439 (18.2%)	RR 1.71 (1.17 to 2.49)	129 more per 1000 (from 31 more to 272 more)	□□□□ LOW	CRITICAL
							25.5%		181 more per 1000 (from 43 more to 380 more)		
Percent change in cerebral volume from baseline (follow-up 52 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	39	38	-	MD 0.2 lower (1.15 lower to 0.75 higher)	□□□□ MODERATE	CRITICAL
Percent change in cerebral volume from baseline (follow-up 104 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	39	33	-	MD 0.59 higher (0.86 lower to 2.04 higher)	□□□□ MODERATE	CRITICAL
Percent change in cerebral volume from baseline (follow-up 156 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	47	43	-	MD 0.5 higher (0.8 lower to 1.8 higher)	□□□□ MODERATE	CRITICAL
Absolute change in brain total lesion volume from baseline (cm3) (follow-up 52 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	329	321	-	MD 2.53 lower (3.22 to 1.84 lower)	□□□□ MODERATE	CRITICAL
Absolute change in brain total lesion volume from baseline (cm3) (follow-up 104 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	308	302	-	MD 3.83 lower (4.92 to 2.74 lower)	□□□□ MODERATE	CRITICAL
Absolute change in brain total lesion volume from baseline (cm3) (follow-up 156 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	334	330	-	MD 4.89 lower (6.11 to 3.67 lower)	□□□□ MODERATE	CRITICAL
Cumulative number of new or enlarging lesions calculated from baseline (follow-up 52 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	350	345	-	MD 2.28 lower (2.93 to 1.63 lower)	□□□□ MODERATE	CRITICAL
Cumulative number of new or enlarging lesions calculated from baseline (follow-up 104 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	350	345	-	MD 4.02 lower (5.09 to 2.95 lower)	□□□□ MODERATE	CRITICAL
Cumulative number of new or enlarging lesions calculated from baseline (follow-up 152 weeks; Better indicated by lower values)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	350	345	-	MD 5.05 lower (6.48 to 3.62 lower)	□□□□ MODERATE	CRITICAL
Number of participants who displayed =>1 active lesion during follow-up (follow-up 156 weeks)											
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	225/350 (64.3%)	289/345 (83.8%)	RR 0.77 (0.7 to 0.84)	193 fewer per 1000 (from 134 fewer to 251 fewer)	□□□□ MODERATE	CRITICAL
							83.8%		193 fewer per 1000 (from 134 fewer to 251 fewer)		

Quality of life (follow-up 156 weeks; measured with: Multiple Sclerosis Quality of Life Inventory (MSQLI); Better indicated by higher values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	310	304	-	MD 0.25 higher (0.16 to 0.34 higher)	□□□□ MODERATE	CRITICAL

[1] Confidence intervals include a negligible effect and appreciable benefit
[2] High risk of performance bias for the North American Study Group 2004 ("Patients and treating physicians were more likely to guess treatment allocation correctly due to side effects"). High risk of bias due to incomplete outcome data (The North American Study Group 2004 - 28% of data missing from analysis - and Andersen 2004 - unequal drop-out between groups). Unclear risk of selective outcome reporting - no protocols located. Unclear risk of selection bias as method of sequence generation and allocation concealment not reported (Andersen 2004).
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] High risk of performance bias for the North American Study Group 2004 ("Patients and treating physicians were more likely to guess treatment allocation correctly due to side effects"). High risk of bias due to incomplete outcome data (The North American Study Group 2004 - 28% of data missing from analysis - and Andersen 2004 - unequal drop-out between groups). Unclear risk of selective outcome reporting - no protocols located. Unclear risk of selection bias as method of sequence generation and allocation concealment not reported (Andersen 2004). Allocation concealment not reported (SPECTRIMS 2001).
[5] Unclear risk of selective outcome reporting - no protocols located. Unclear risk of selection bias as method of sequence generation and allocation concealment not reported (Andersen 2004). Allocation concealment not reported (SPECTRIMS 2001).
[6] High risk of performance bias for the North American Study Group 2004 ("Patients and treating physicians were more likely to guess treatment allocation correctly due to side effects"). High risk of bias due to incomplete outcome data (The North American Study Group 2004 - 28% of data missing from analysis).
[7] Unclear risk of selective outcome reporting (no protocol located). Allocation concealment unclear.
[8] Unclear risk of selective outcome reporting (unable to locate study protocol)
[9] High risk of performance bias ("Patients and treating physicians were more likely to guess treatment allocation correctly due to side effects"). High risk of bias due to incomplete outcome data. Unclear risk of selective outcome reporting - no protocol located.

16. Mitoxantrone compared with placebo for secondary progressive multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mitoxantrone	Placebo	Relative (95% CI)	Absolute		
Disability progression sustained at 3 months (follow-up 104 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/60 (8.3%)	14/64 (21.9%)	RR 0.38 (0.15 to 0.99)	136 fewer per 1000 (from 2 fewer to 186 fewer)	⊕⊕OO LOW	CRITICAL
								21.9%		136 fewer per 1000 (from 2 fewer to 186 fewer)		
Participants wheelchair bound (follow-up 104 weeks; assessed with: EDSS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/60 (5%)	7/64 (10.9%)	RR 0.46 (0.12 to 1.69)	59 fewer per 1000 (from 96 fewer to 75 more)	⊕⊕OO LOW	CRITICAL
								10.9%		59 fewer per 1000 (from 96 fewer to 75 more)		
Discontinuation due to any reason (follow-up 104 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/63 (23.8%)	18/65 (27.7%)	RR 0.86 (0.48 to 1.55)	39 fewer per 1000 (from 144 fewer to 152 more)	⊕⊕OO LOW	CRITICAL
								27.7%		39 fewer per 1000 (from 144 fewer to 152 more)		
Discontinuation due to side effects (follow-up 104 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/63 (7.9%)	2/65 (3.1%)	RR 2.58 (0.52 to 12.81)	49 more per 1000 (from 15 fewer to 363 more)	⊕⊕OO LOW	CRITICAL
								3.1%		49 more per 1000 (from 15 fewer to 366 more)		

[1] Allocation concealment was unclear from the published report. High risk of incomplete outcome data - 27% of the sample were withdrawn from the study prior to trial completion. Unclear risk of selective outcome reporting as no study protocol was available.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Review question 3

1. Interferon vs placebo for primary progressive multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Placebo	Relative (95% CI)	Absolute		
Disability progression confirmed at 3 months (number of participants) (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/51 (39.2%)	24/57 (42.1%)	RR 0.97 (0.62 to 1.52)	13 fewer per 1000 (from 160 fewer to 219 more)	⊕⊕OO LOW	CRITICAL
								42.8%		13 fewer per 1000 (from 163 fewer to 223 more)		
Disability progression confirmed at 6 months (number of participants) (follow-up 104 weeks)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	8/36 (22.2%)	12/37 (32.4%)	RR 0.69 (0.32 to 1.48)	101 fewer per 1000 (from 221 fewer to 156 more)	⊕⊕OO LOW	CRITICAL
								32.4%		100 fewer per 1000 (from 220 fewer to 156 more)		
Discontinuation of study drug due to any reason (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/51 (5.9%)	5/57 (8.8%)	RR 1.03 (0.93 to 1.14)	3 more per 1000 (from 6 fewer to 12 more)	⊕⊕OO LOW	IMPORTANT
								9.1%		3 more per 1000 (from 6 fewer to 13 more)		
Discontinuation of study drug due to side effects (follow-up 104 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/15 (6.7%)	0/20 (0%)	RR 0.93 (0.78 to 1.1)	-	⊕⊕OO LOW	IMPORTANT
								0%		-		
Discontinuation due to any reason (follow-up 104 weeks)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/51 (2%)	2/57 (3.5%)	RR 1.02 (0.95 to 1.09)	1 more per 1000 (from 2 fewer to 3 more)	⊕⊕OO LOW	IMPORTANT
								2.7%		1 more per 1000 (from 1 fewer to 2 more)		
Mortality (follow-up 104 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/36 (0%)	1/37 (2.7%)	RR 1.03 (0.95 to 1.11)	1 more per 1000 (from 1 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.7%		1 more per 1000 (from 1 fewer to 3 more)		

[1] High risk of detection bias (Leary 2003). Unclear allocation concealment and risk of selective outcome reporting (Leary 2003).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Unclear allocation concealment

2. Glatiramer acetate vs placebo for primary progressive multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Glatiramer acetate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression (number of participants) (follow-up median 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	248/627 (39.6%)	143/316 (45.3%)	RR 0.87 (0.75 to 1.02)	59 fewer per 1000 (from 113 fewer to 9 more)	□□□□ MODERATE	CRITICAL
								45.3%		59 fewer per 1000 (from 113 fewer to 9 more)		
Time to disability progression												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	248/627 (39.6%)	143/316 (45.3%)	HR 0.87 (0.71 to 1.07)	45 fewer per 1000 (from 105 fewer to 23 more)	□□□□ MODERATE	IMPORTANT
								45.3%		45 fewer per 1000 (from 105 fewer to 23 more)		
Discontinuation of drug due to any reason (156 weeks' follow-up)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/627 (35.6%)	116/316 (36.7%)	RR 0.97 (0.81 to 1.16)	11 fewer per 1000 (from 70 fewer to 59 more)	□□□□ MODERATE	IMPORTANT
								36.7%		11 fewer per 1000 (from 70 fewer to 59 more)		
Discontinuation of drug due to side effects (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/627 (7.7%)	10/316 (3.2%)	RR 2.42 (1.24 to 4.72)	45 more per 1000 (from 8 more to 118 more)	□□□□ LOW	IMPORTANT
								3.2%		45 more per 1000 (from 8 more to 119 more)		
Mortality (risk of non-event) (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/627 (0.6%)	7/316 (2.2%)	RR 1.02 (1 to 1.03)	0 more per 1000 (from 0 more to 1 more)	□□□□ LOW	IMPORTANT
								2.2%		0 more per 1000 (from 0 more to 1 more)		

[1] Unclear risk of selection bias (authors did not describe method for generating the randomisation sequence or allocation of participants to intervention groups). Unclear risk of selective outcome reporting as study protocol was not located.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

3. Fingolimod vs placebo for primary progressive multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fingolimod**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Disability progression (number of participants) (3 criteria) (follow-up 156 weeks)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	232/336 (69%)	338/487 (69.4%)	RR 0.99 (0.91 to 1.09)	7 fewer per 1000 (from 62 fewer to 62 more)	□□□□ MODERATE	CRITICAL
								69.4%		7 fewer per 1000 (from 62 fewer to 62 more)		
Disability progression (number of participants) (1 criterion) (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/336 (45.8%)	240/487 (49.3%)	RR 0.93 (0.8 to 1.08)	34 fewer per 1000 (from 99 fewer to 39 more)	□□□□ MODERATE	CRITICAL
								49.3%		35 fewer per 1000 (from 99 fewer to 39 more)		
Discontinuation of study drug due to side effects (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/336 (15.5%)	36/487 (7.4%)	RR 2.09 (1.4 to 3.13)	81 more per 1000 (from 30 more to 157 more)	□□□□ LOW	IMPORTANT
								7.4%		81 more per 1000 (from 30 more to 158 more)		
Mortality (risk of non-event) (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/336 (0.3%)	2/487 (0.4%)	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 0 fewer to 0 more)	□□□□ LOW	IMPORTANT
								0.4%		0 fewer per 1000 (from 0 fewer to 0 more)		
Cancer (number of participants with any neoplasm) (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/336 (7.7%)	12/487 (2.5%)	RR 3.14 (1.61 to 6.14)	53 more per 1000 (from 15 more to 127 more)	□□□□ LOW	IMPORTANT
								2.5%		54 more per 1000 (from 15 more to 128 more)		
Infection (number of participants with any infection) (follow-up 156 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/336 (40.8%)	215/487 (44.1%)	RR 0.92 (0.78 to 1.09)	35 fewer per 1000 (from 97 fewer to 40 more)	□□□□ MODERATE	IMPORTANT
								44.2%		35 fewer per 1000 (from 97 fewer to 40 more)		
Discontinuation due to any reason (follow-up 156 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	116/336 (34.5%)	170/487 (34.9%)	RR 0.99 (0.82 to 1.2)	3 fewer per 1000 (from 63 fewer to 70 more)	□□□□ MODERATE	IMPORTANT
								34.9%		3 fewer per 1000 (from 63 fewer to 70 more)		

[1] High risk of attrition bias (39% of participants were lost to follow-up)
[2] Optimal information size

4. Ocrelizumab compared with placebo for primary progressive multiple sclerosis

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ocrelizumab	Placebo	Relative (95% CI)	Absolute		
Time to disability progression (confirmed at 12 weeks) (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.76 (0.59 to 0.98)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Time to disability progression (confirmed at 24 weeks) (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.75 (0.58 to 0.97)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Discontinuation of drug due to any reason (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	96/488 (19.7%)	80/244 (32.8%)	RR 0.6 (0.47 to 0.77)	131 fewer per 1000 (from 75 fewer to 174 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								32.8%		131 fewer per 1000 (from 75 fewer to 174 fewer)		
Mortality (risk of non-event) (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	4/486 (0.8%)	1/239 (0.4%)	RR 1 (0.98 to 1.01)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.4%		0 fewer per 1000 (from 0 fewer to 0 more)		
Malignancies - number of participants (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/486 (2.3%)	2/239 (0.8%)	RR 2.7 (0.6 to 12.11)	14 more per 1000 (from 3 fewer to 93 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.8%		14 more per 1000 (from 3 fewer to 89 more)		
Neoplasms (any) - number of participants (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/486 (1.6%)	7/239 (2.9%)	RR 0.56 (0.21 to 1.53)	13 fewer per 1000 (from 23 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.9%		13 fewer per 1000 (from 23 fewer to 15 more)		
Serious adverse events (at least 1) - number of participants (follow-up 120 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	99/486 (20.4%)	53/239 (22.2%)	RR 0.92 (0.68 to 1.23)	18 fewer per 1000 (from 71 fewer to 51 more)	⊕⊕⊕O MODERATE	CRITICAL
								22.2%		18 fewer per 1000 (from 71 fewer to 51 more)		

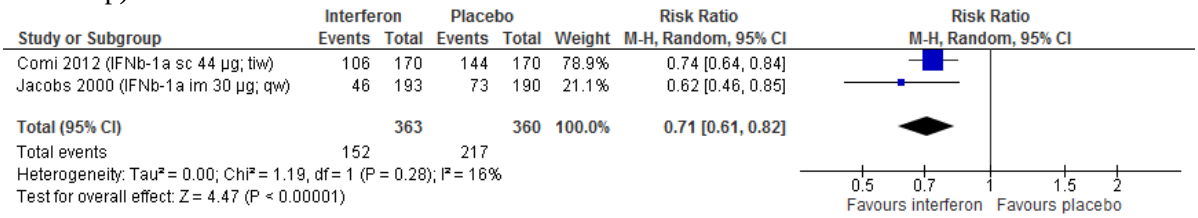
[1] Confidence intervals include a negligible effect and appreciable benefit
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Appendix 6_ Forest plots

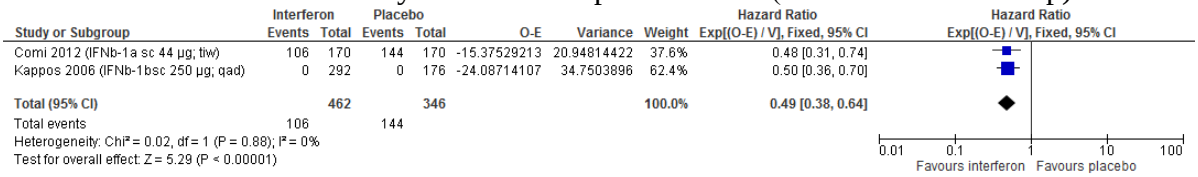
Review question 1

1. Interferon compared with placebo

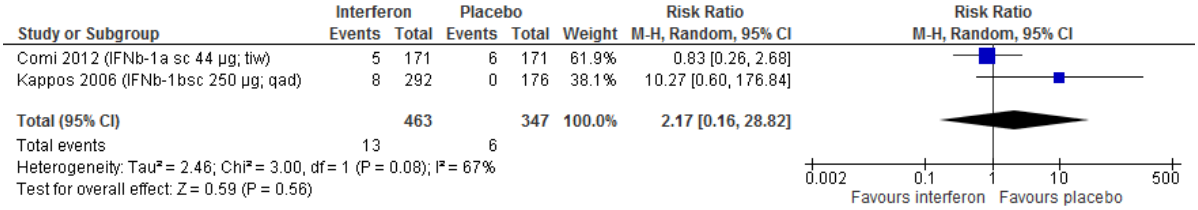
Conversion to clinically definite multiple sclerosis [1] – number of participants (104 weeks' follow-up)



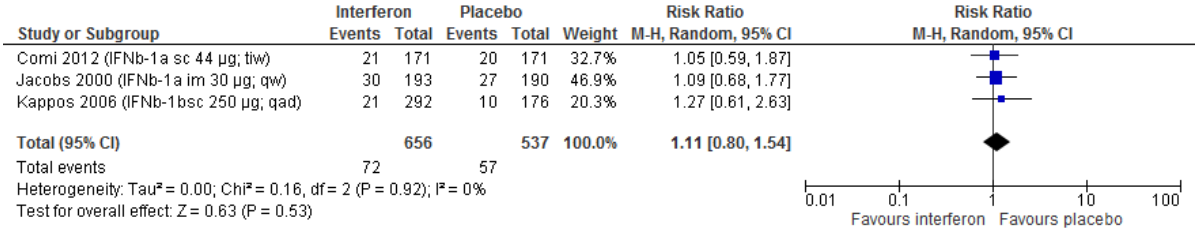
Time to conversion to clinically definite multiple sclerosis[2] (104 weeks' follow-up)



Tolerability/side effects - discontinuation due to side effects (104 weeks' follow-up)



Tolerability/side effects - discontinuation due to any reason (104 weeks' follow-up)



Tolerability/side effects - discontinuation of study drug due to side effects (104 weeks' follow-up)

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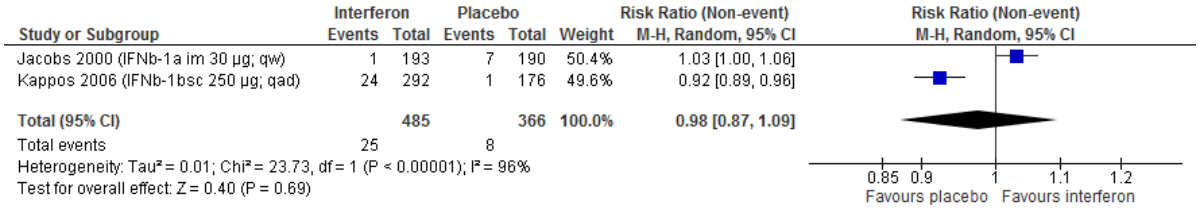
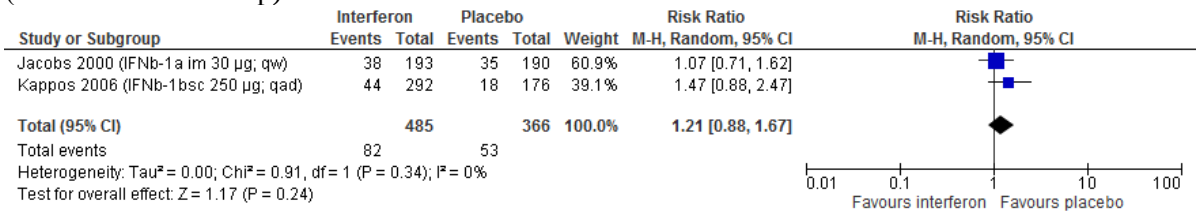
[1] Comi 2012: To meet the McDonald criteria for diagnosis of MS, patients had to have evidence of spatial and temporal dissemination of MRI lesions or a second clinical attack. For patients without a second attack, MRI follow-up scans were assessed and lesions were classified qualitatively as persisting, new, or enlarging and the location recorded as infratentorial, juxtacortical, periventricular, or deep white matter. Dissemination in space on MRI was defined as three of the following: at least one gadolinium-enhancing lesion or at least nine T2 hyper-intense lesions; at least one infratentorial lesion; at least one juxtacortical lesion; or at least three periventricular lesions. Alternatively, dissemination in space could be defined as at least two MRI lesions consistent with MS plus positive CSF. Dissemination in time was defined as a new gadolinium enhancing lesion more than 3 months after onset of the first clinical demyelinating event (at a site different from the initial event) or a new T2 lesion at any time compared with a scan at least 30 days after the onset of the initial clinical event.

Jacobs 2000: Defined as (1) the occurrence of a new symptomatic neurological event attributable to a different part of the CNS than the initial episode (prior to CHAMPS study entry) and in the absence of fever or infection lasting more than 48 hours (2) symptomatic progressive neurologic deterioration, defined as an increase of 1.5 points in Expanded Disability Status Scale score. CDMS required confirmation by an independent blinded outcomes committee

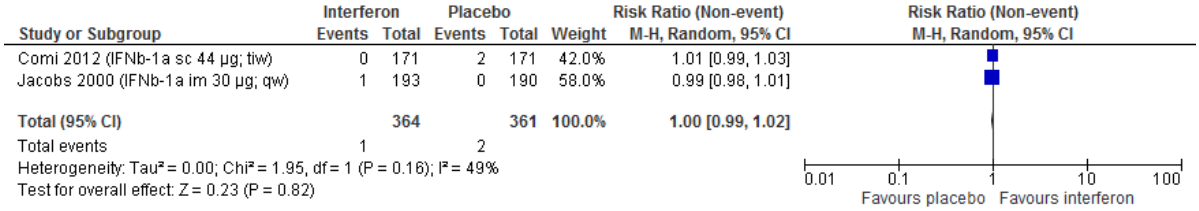
[2] Kappos 2006: CDMS was defined according to slightly modified Poser criteria by 1) a relapse with clinical evidence of at least one CNS lesion, and if the first presentation was monofocal distinct from the lesion responsible for the CIS presentation, or 2) sustained progression by 1.5 points on the EDSS reaching a total EDSS score of 2.5 and confirmed at a consecutive visit 3 months later.



Tolerability/side effects - discontinuation of study drug due to any reason (risk of non-event) (104 weeks' follow-up)



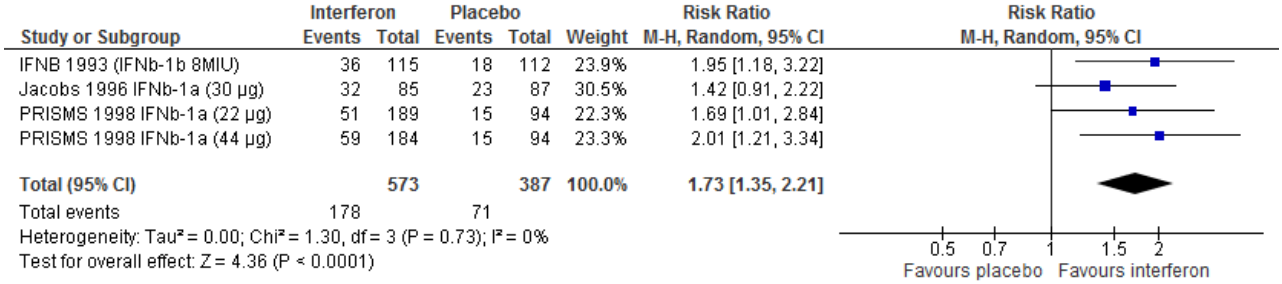
Mortality (risk of non-event) (104 weeks' follow-up)



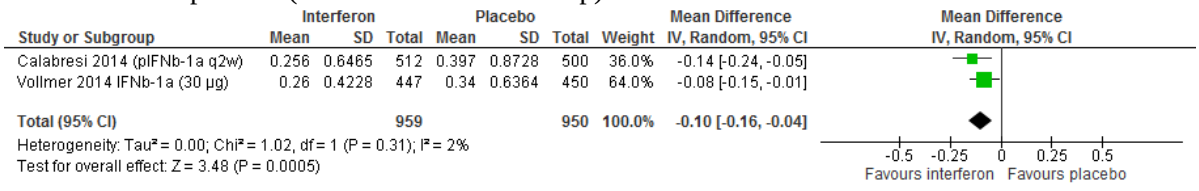
Review question 2

1. Interferon compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

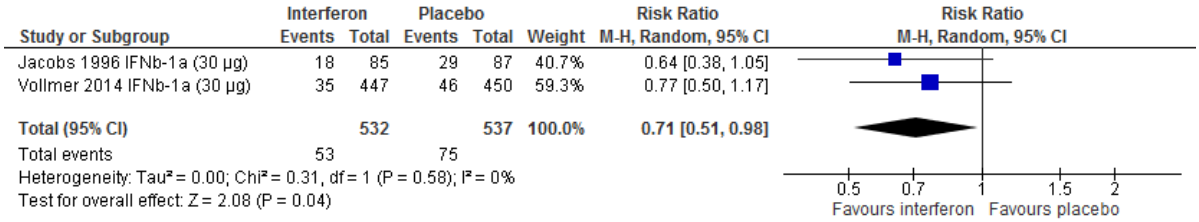


Annualised relapse rate (48-104 weeks' follow-up)

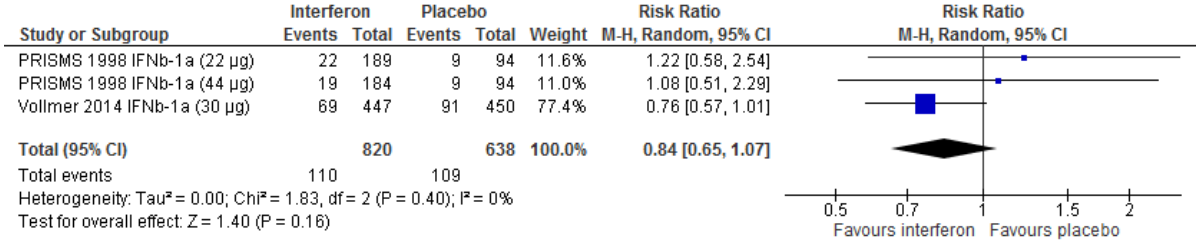


Disability progression[3] – number of participants worsened (104 weeks' follow-up)

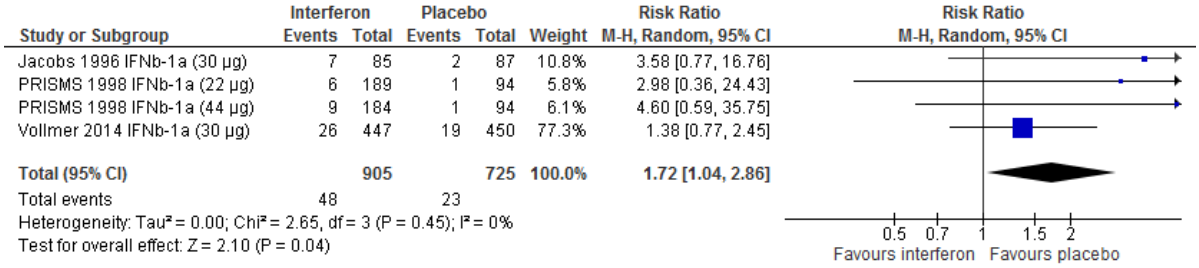
[3] Jacobs 1996: Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months
Vollmer 2014: defined as a 1.0 point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 6 months



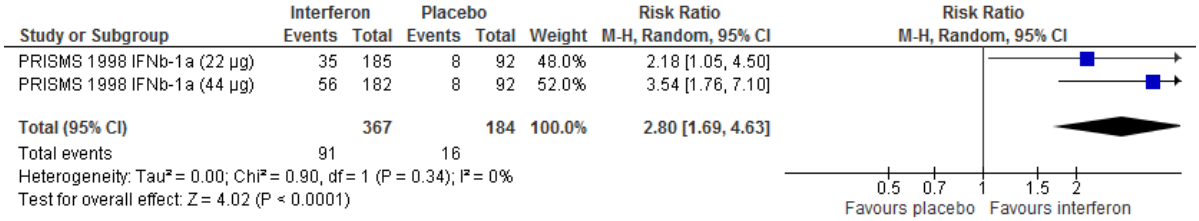
Discontinuation due to any reason (104 weeks' follow-up)



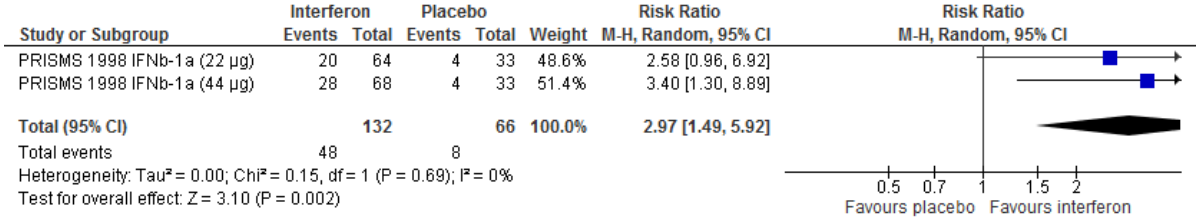
Discontinuation due to side effects (104 weeks' follow-up)



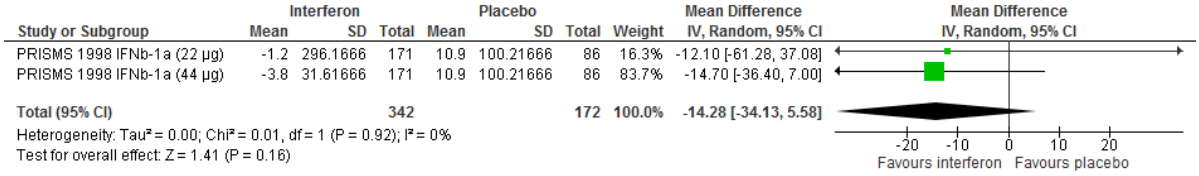
T2 active lesions – number of participants with no activity (104 weeks' follow-up)



Combined unique active lesions - number of participants with no activity (104 weeks' follow-up)

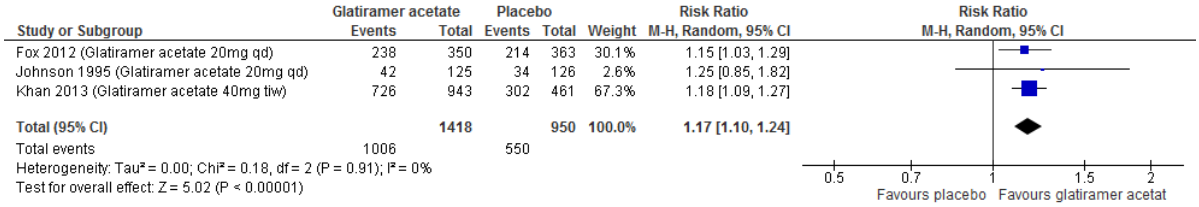


Burden of disease (percent change from baseline of total areas of all MS lesions; mm2) - 104 weeks follow-up

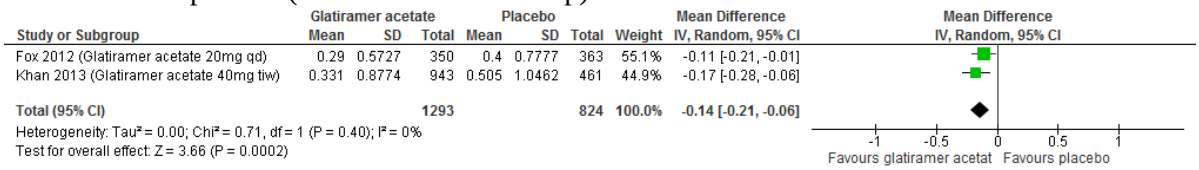


2. Glatiramer acetate compared with placebo

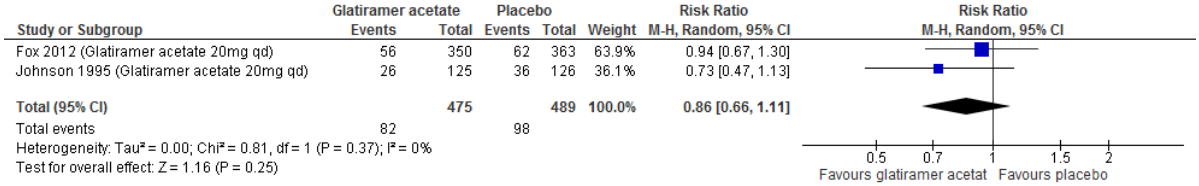
Relapse - number of participants relapse free (52-104 weeks' follow-up)



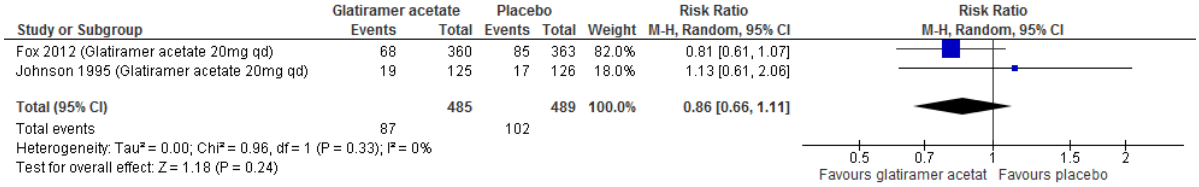
Annualised relapse rate (52-96 weeks' follow-up)



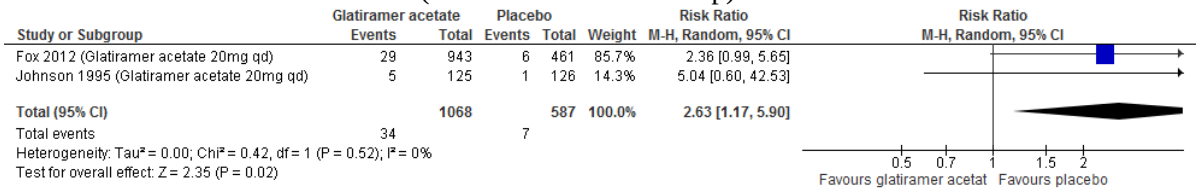
Disability progression[4] – number of participants worsened (96-104 weeks' follow-up)



Discontinuation due to any reason (96-104 weeks' follow-up)

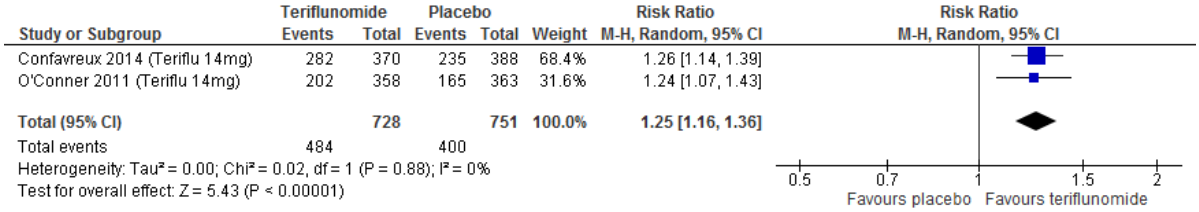


Discontinuation due to side effects (96-104 weeks' follow-up)



3. Teriflunomide compared with placebo

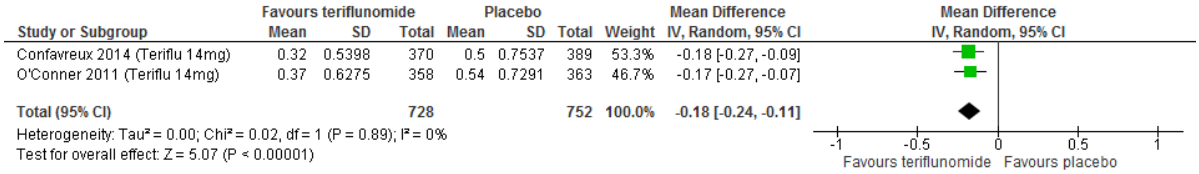
Relapse - number of participants relapse free (48-108 weeks' follow-up)



Annualised relapse rate (48-108 weeks' follow-up)

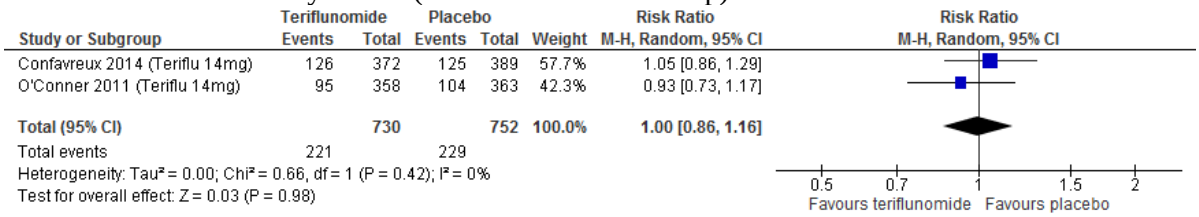
[4] Fox 2012: defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later

Johnson 1995: EDSS increase of at least 1 point sustained at 3 months

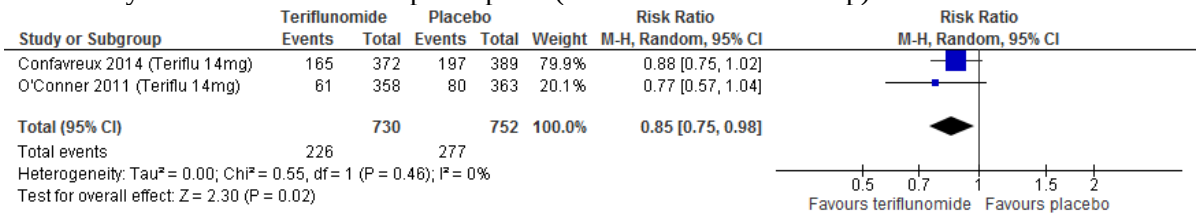


Disability progression[5] – number of participants worsened (48-108 weeks' follow-up)

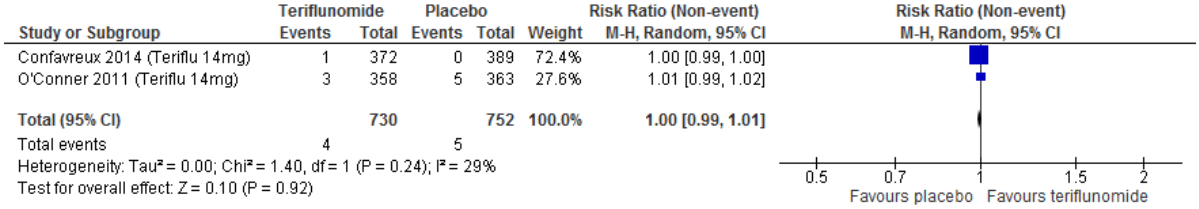
Discontinuation due to any reason (48-108 weeks' follow-up)



Risk of any infection – number of participants (48-108 weeks' follow-up)

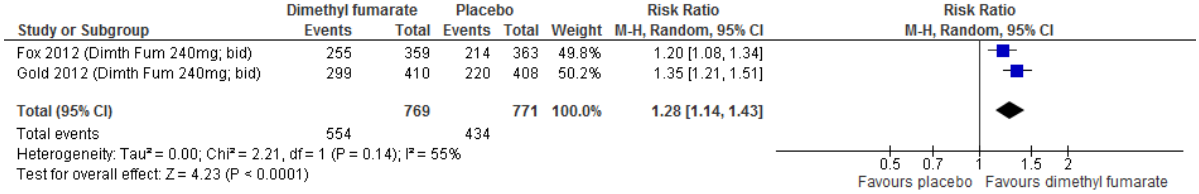


Risk of cancer – number of participants with any neoplasm (risk of non-event) (48-108 weeks' follow-up)

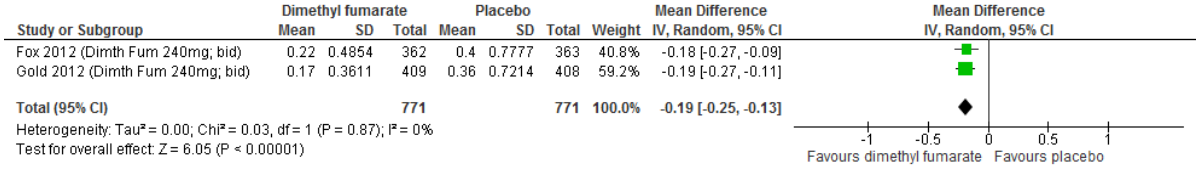


4. Dimethyl fumarate compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

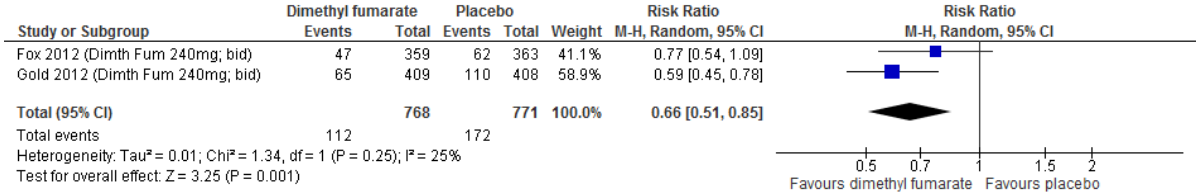


Annualised relapse rate (104 weeks' follow-up)

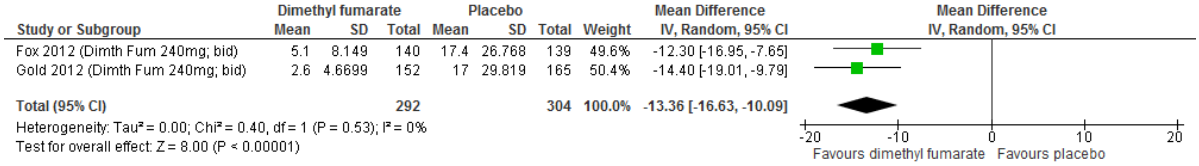


[5] Sustained disability progression was defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks

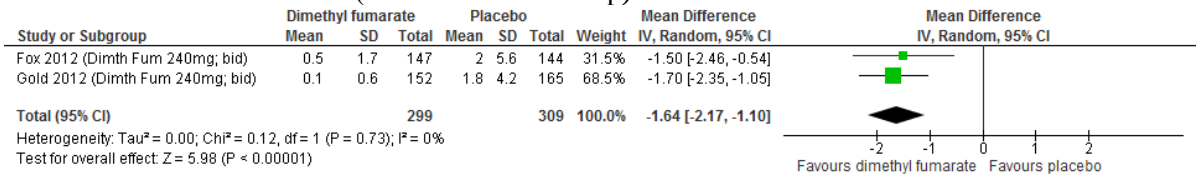
Disability progression[6] – number of participants worsened (104 weeks' follow-up)



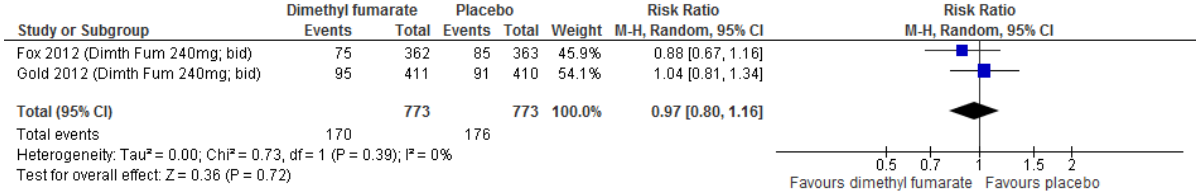
New or newly enlarging T2 lesions – mean number (104 weeks' follow-up)



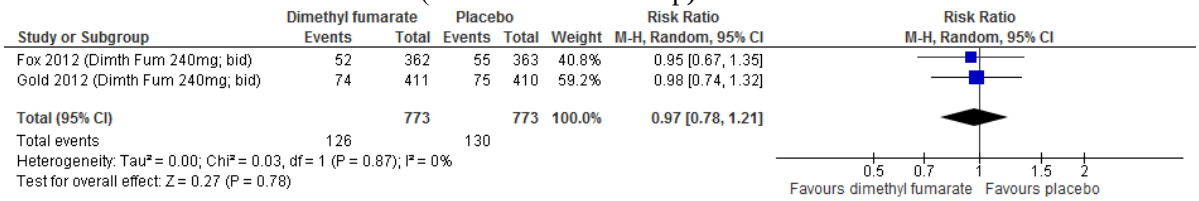
GAD lesions – mean number (104 weeks' follow-up)



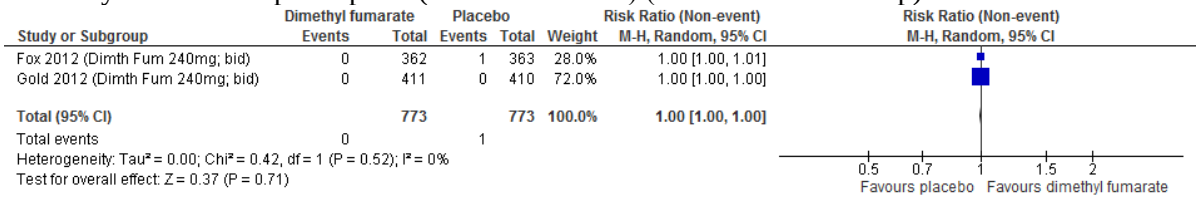
Discontinuation due to any reason (104 weeks' follow-up)



Discontinuation due to side effects (104 weeks' follow-up)



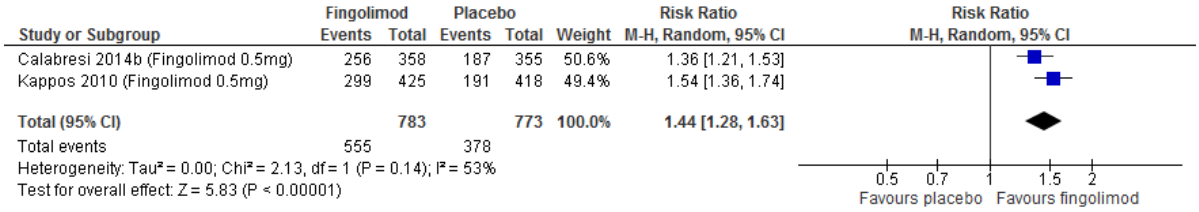
Mortality – number of participants (risk of non-event) (104 weeks' follow-up)



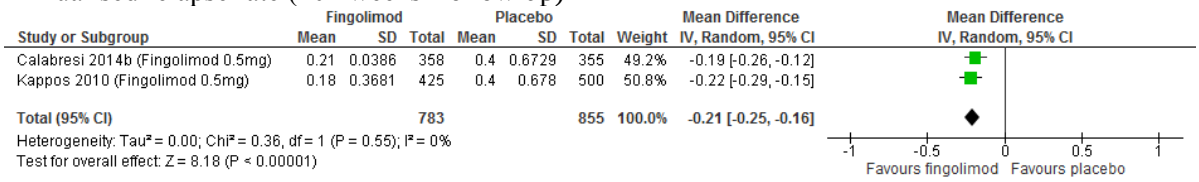
5. Fingolimod compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

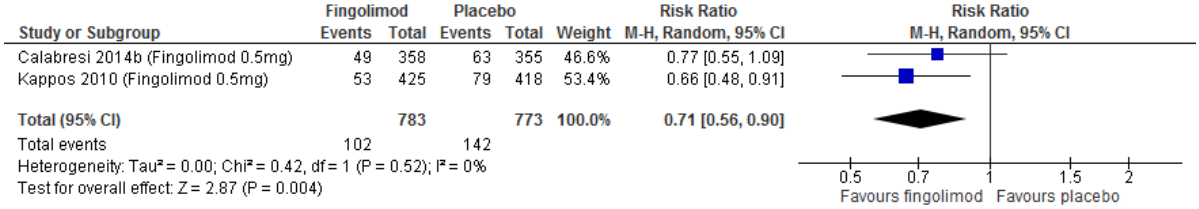
[6] Defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later



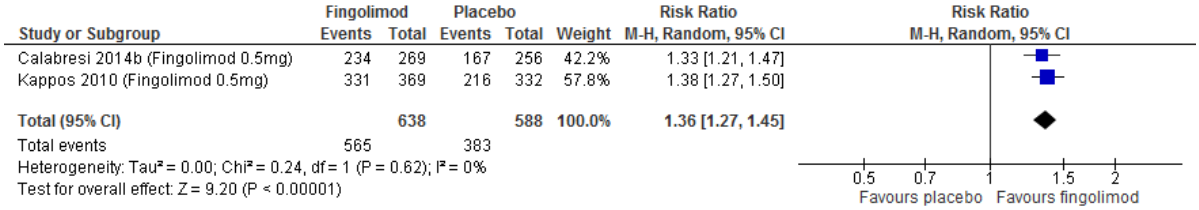
Annualised relapse rate (104 weeks' follow-up)



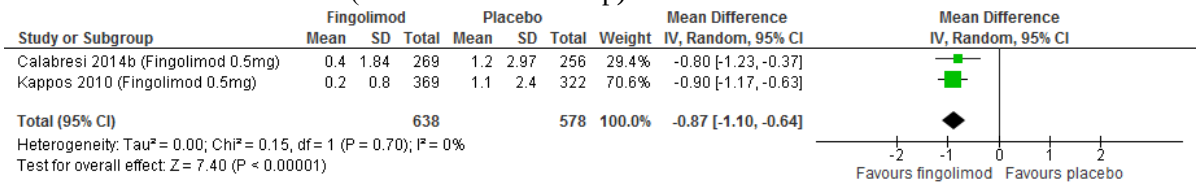
Disability progression[7] – number of participants worsened (104 weeks' follow-up)



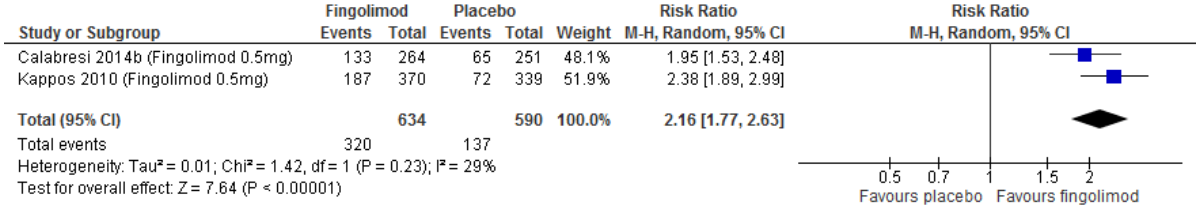
GAD lesions – number of participants with no lesions (104 weeks' follow-up)



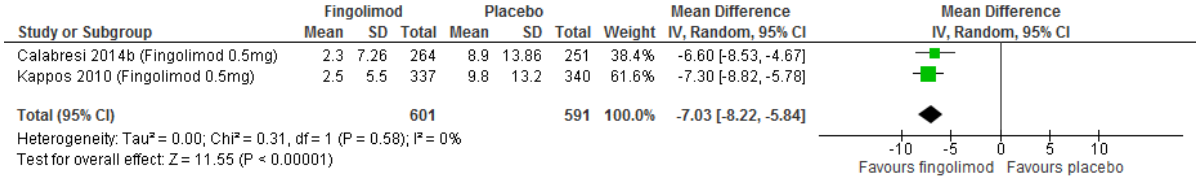
GAD lesions - mean number (104 weeks' follow-up)



New or newly enlarged T2 lesions (number of patients with no lesions)

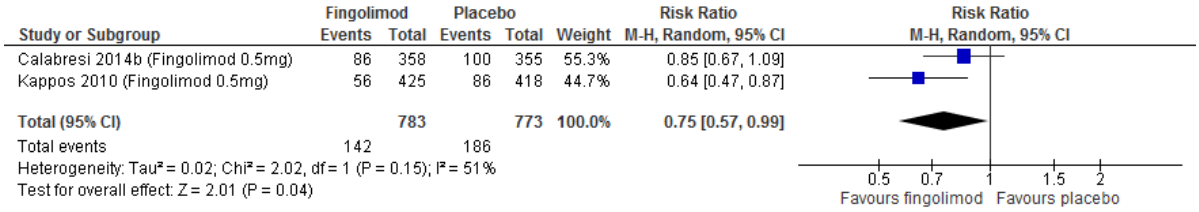


New or newly enlarging T2 lesions – mean number (104 weeks' follow-up)

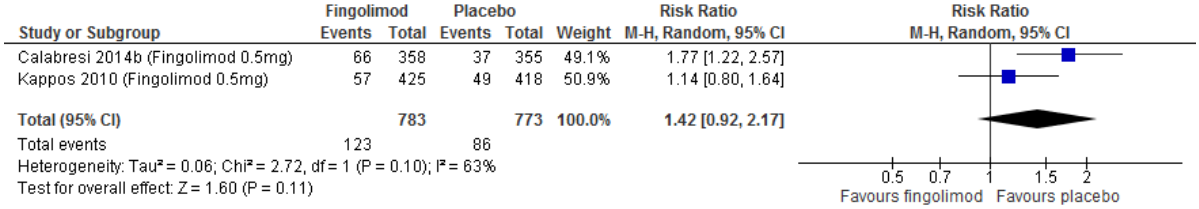


Discontinuation due to any reason (104 weeks' follow-up)

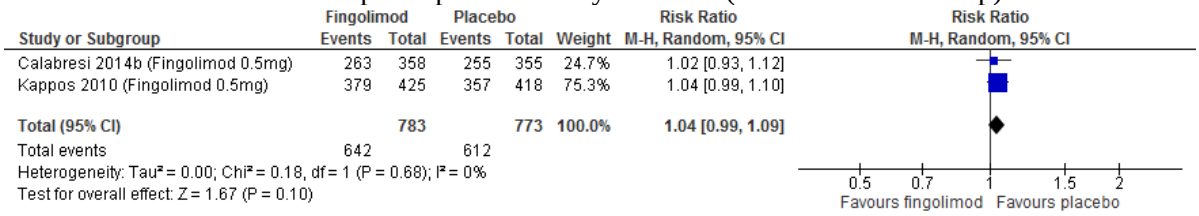
[7] Calabresi 2014b: defined as a 1 point EDSS change (0·5 point if baseline EDSS was >5·0)
Kappos 2010: Defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.



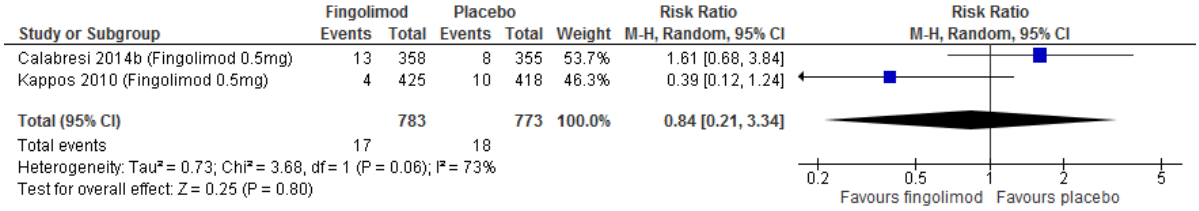
Discontinuation due to side effects (104 weeks' follow-up)



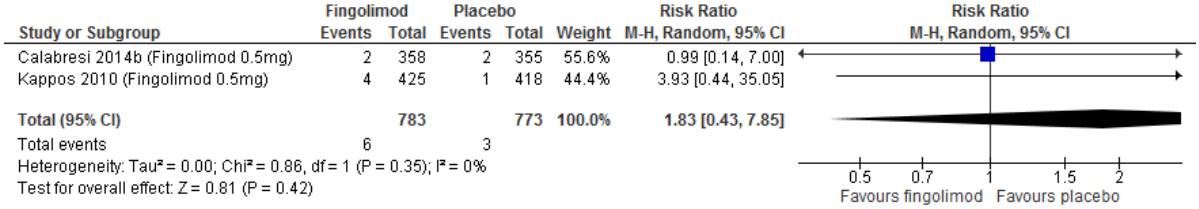
Risk of infection – number of participants with any infection (104 weeks' follow-up)



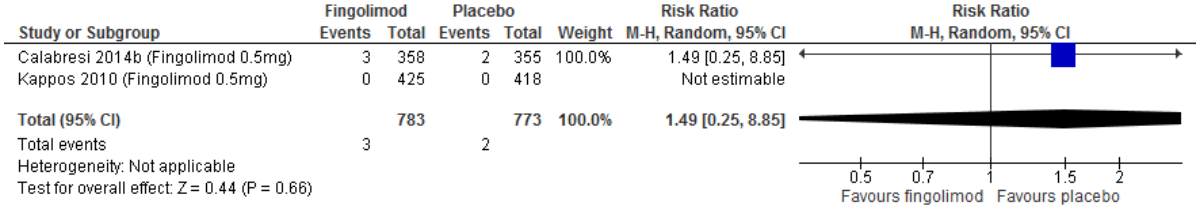
Risk of cancer – number of participants with any neoplasm (104 weeks' follow-up)



Risk of bradycardia – number of participants (104 weeks' follow-up)



Risk of macular edema – number of participants (104 weeks' follow-up)

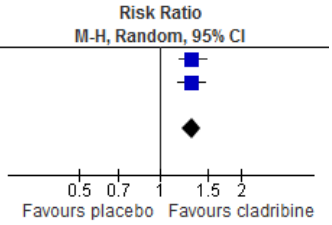


6. Cladribine compared with placebo

Relapse - number of participants relapse free (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	345	433	133	219	50.0%	1.31 [1.17, 1.47]
Giovannoni 2010 (Cladribine 5.25mg/kg)	360	456	133	219	50.0%	1.30 [1.16, 1.46]
Total (95% CI)		**889**		**438**	**100.0%**	**1.31 [1.20, 1.42]**
Total events	705		266			

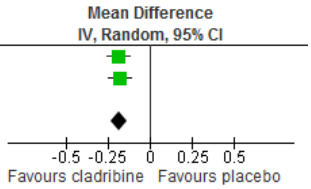
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 6.35 (P < 0.00001)



Annualised relapse rate (96 weeks' follow-up)

Study or Subgroup	Cladribine Mean	Cladribine SD	Cladribine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	0.14	0.2653	433	0.33	0.48	219	50.0%	-0.19 [-0.26, -0.12]
Giovannoni 2010 (Cladribine 5.25mg/kg)	0.15	0.2723	456	0.33	0.48	219	50.0%	-0.18 [-0.25, -0.11]
Total (95% CI)			**889**			**438**	**100.0%**	**-0.19 [-0.23, -0.14]**

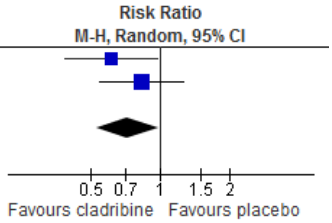
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 7.51 (P < 0.00001)



Discontinuation due to any reason (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	35	433	29	219	45.9%	0.61 [0.38, 0.97]
Giovannoni 2010 (Cladribine 5.25mg/kg)	50	456	29	219	54.1%	0.83 [0.54, 1.27]
Total (95% CI)		**889**		**438**	**100.0%**	**0.72 [0.53, 0.99]**
Total events	85		58			

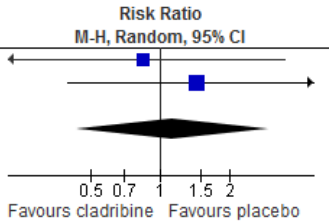
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)



Discontinuation due to side effects (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	5	433	3	219	45.4%	0.84 [0.20, 3.49]
Giovannoni 2010 (Cladribine 5.25mg/kg)	9	456	3	219	54.6%	1.44 [0.39, 5.27]
Total (95% CI)		**889**		**438**	**100.0%**	**1.13 [0.43, 2.94]**
Total events	14		6			

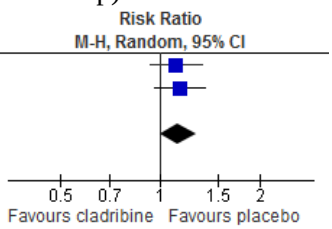
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



Risk of infection – number of participants with any infection (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	205	430	93	218	49.3%	1.12 [0.93, 1.34]
Giovannoni 2010 (Cladribine 5.25mg/kg)	222	454	93	218	50.7%	1.15 [0.96, 1.37]
Total (95% CI)		**884**		**436**	**100.0%**	**1.13 [1.00, 1.29]**
Total events	427		186			

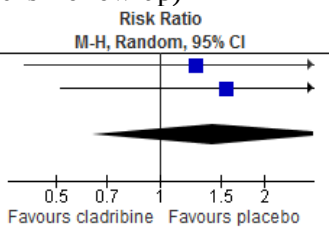
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)



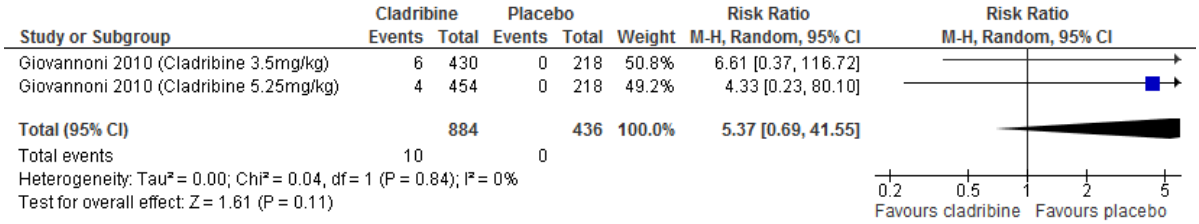
Risk of infection – number of participants with a serious infection (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	10	430	4	218	48.3%	1.27 [0.40, 3.99]
Giovannoni 2010 (Cladribine 5.25mg/kg)	13	454	4	218	51.7%	1.56 [0.51, 4.73]
Total (95% CI)		**884**		**436**	**100.0%**	**1.41 [0.64, 3.13]**
Total events	23		8			

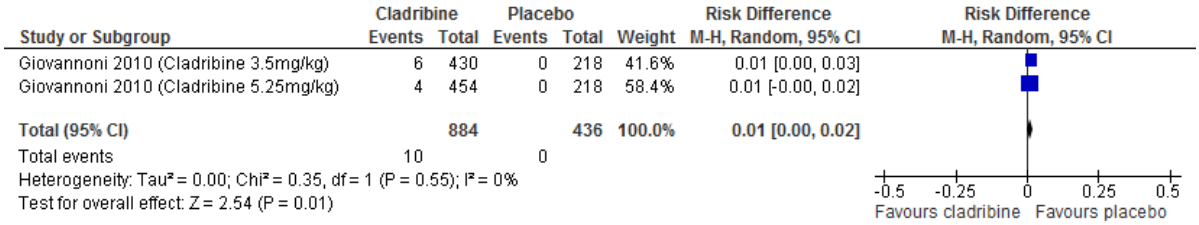
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)



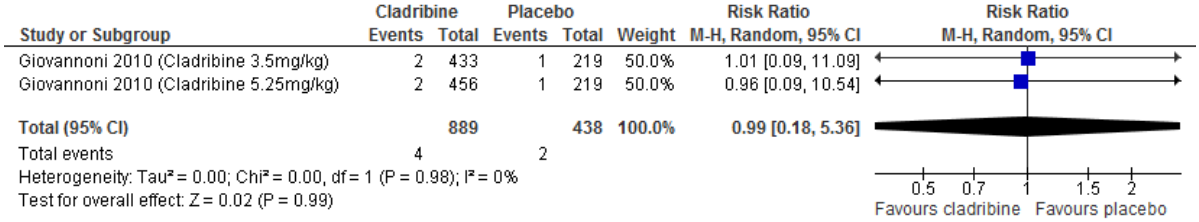
Risk of cancer – number of participants with any neoplasm (96 weeks' follow-up)



Risk difference of cancer – number of participants with any neoplasm (96 weeks' follow-up)

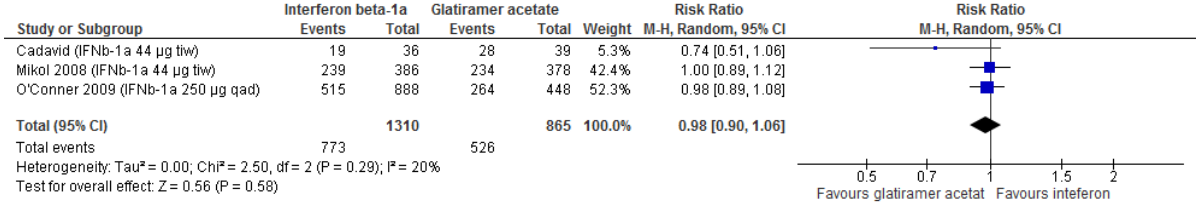


Mortality – number of participants who died (96 weeks' follow-up)

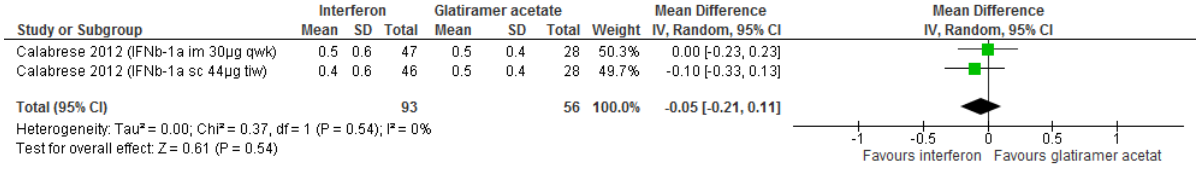


7. Interferon compared with glatiramer acetate

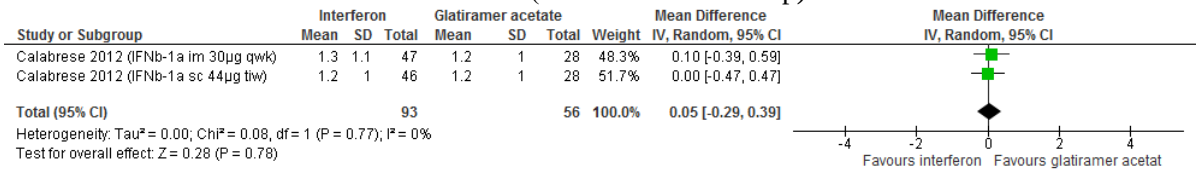
Relapse - number of participants relapse free (96-104 weeks' follow-up)



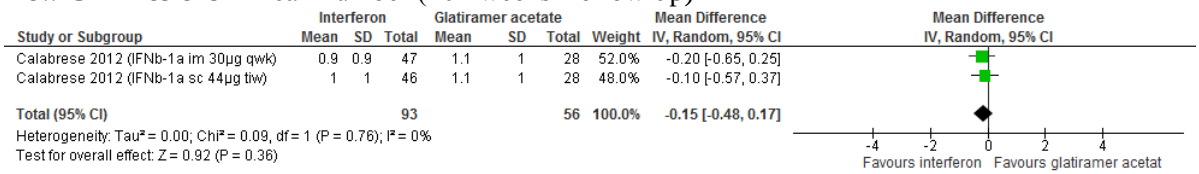
Annualised relapse rate (96-104 weeks' follow-up)



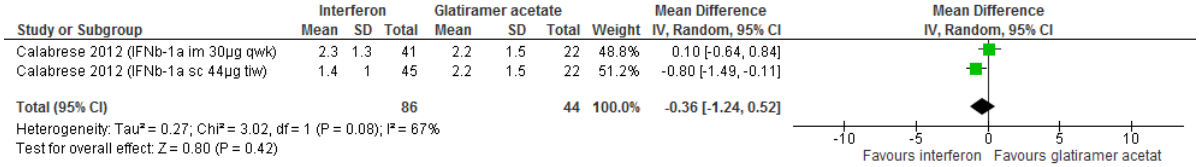
New T2 white matter lesion – mean number (104 weeks' follow-up)



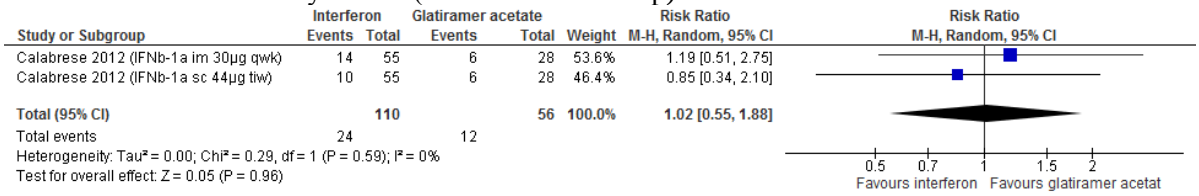
New GAD lesions – mean number (104 weeks' follow-up)



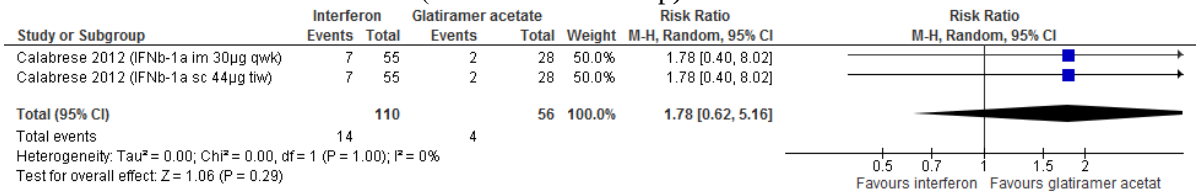
New cortical lesions - mean number (48 months follow-up)



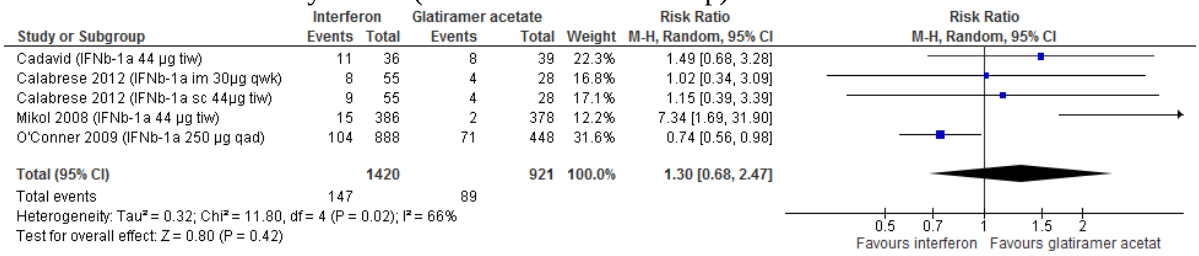
Discontinuation due to any reason (48 weeks' follow-up)



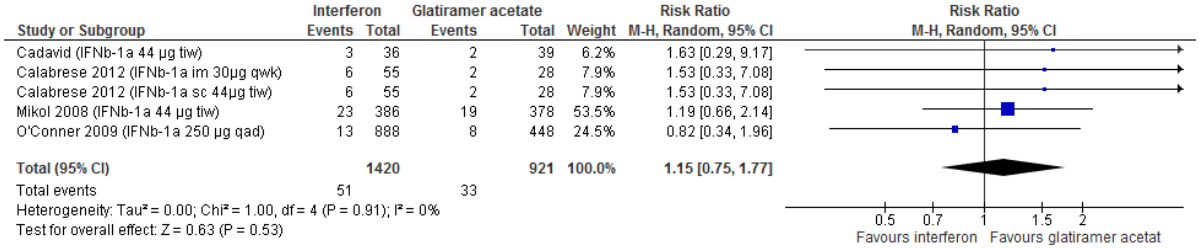
Discontinuation due to side effects (48 weeks' follow-up)



Discontinuation due to any reason (96-104 weeks' follow-up)

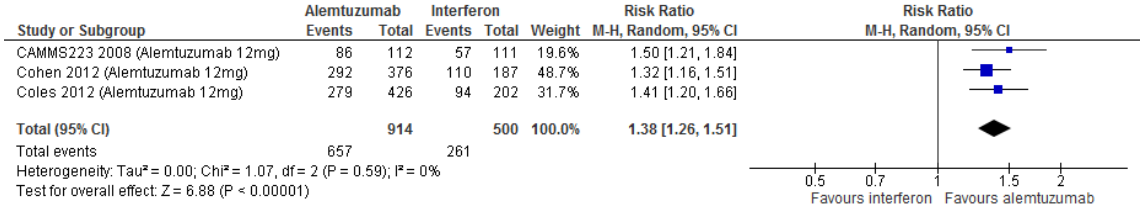


Discontinuation due to side effects (96-104 weeks' follow-up)

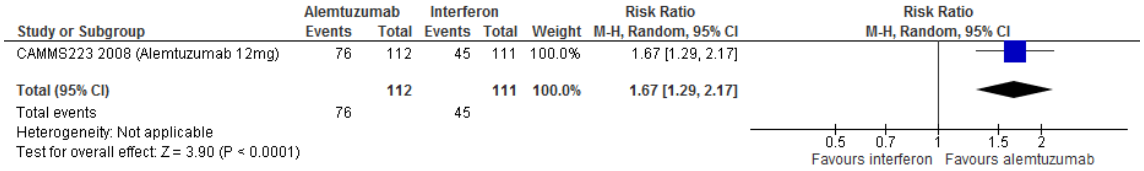


8. Alemtuzumab compared with interferon

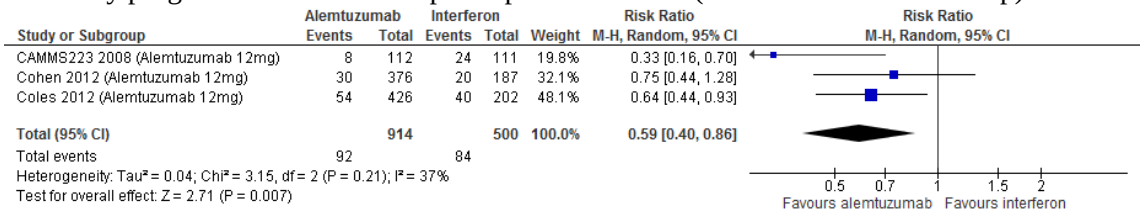
Relapse - number of participants relapse free (104-156 weeks' follow-up)



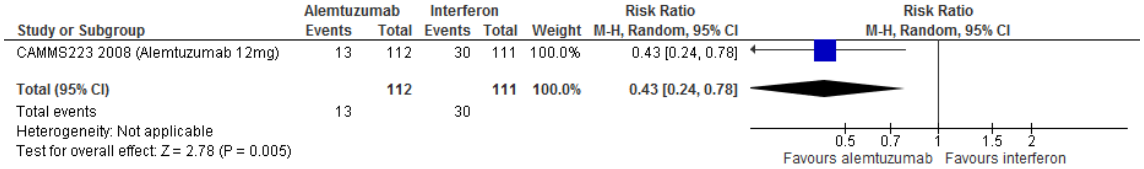
Relapse - number of participants relapse free (260 weeks' follow-up)



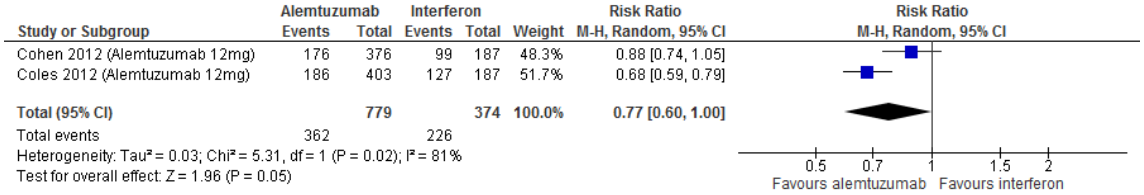
Disability progression[8] – number of participants worsened (104-156 weeks' follow-up)



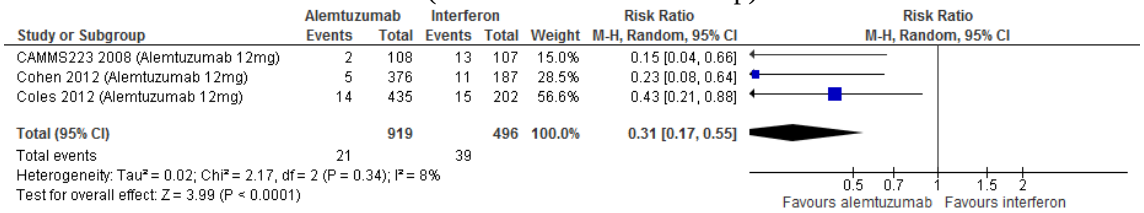
Disability progression - number of participants worsened (260 weeks' follow-up)



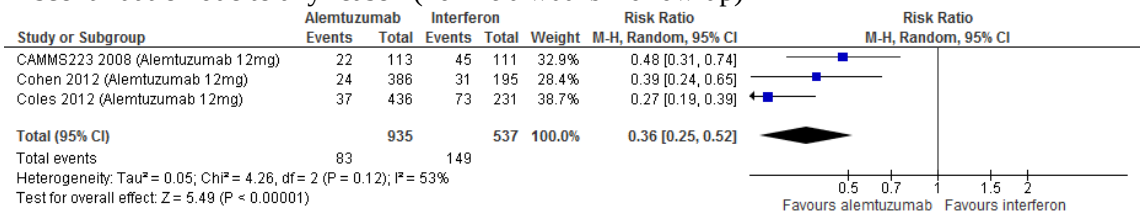
New or enlarging T2-hyperintense lesions – number of participants (104 weeks' follow-up)



Discontinuation due to side effects (104-156 weeks' follow-up)



Discontinuation due to any reason (104-156 weeks' follow-up)

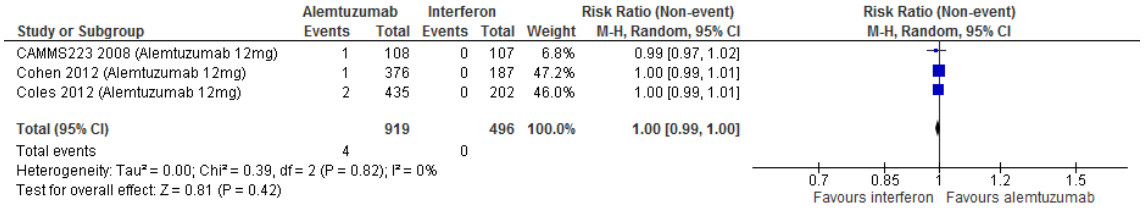


Mortality – number of participants (risk of non-event) (104-156 weeks' follow-up)

[8] Coles 2012: Defined as a decrease from baseline by at least one EDSS point confirmed over 6 months for patients with baseline EDSS scores of at least 2·0

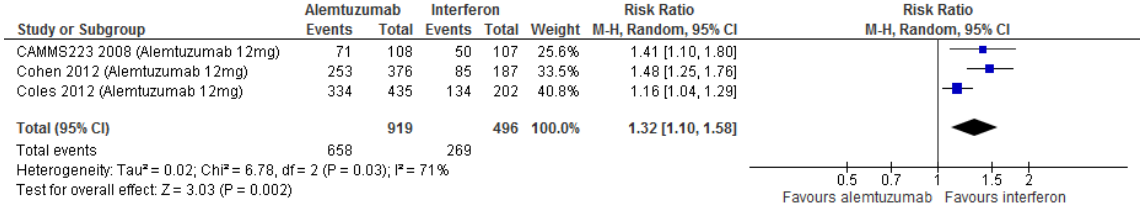
Cohen 2012: Defined as sustained accumulation of disability was defined as an increase from baseline of at least one EDSS point (or ≥1·5 points if baseline EDSS score was 0) confirmed over 6 months

CAMMS223 2011: A sustained accumulation of disability was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more at 6 months.

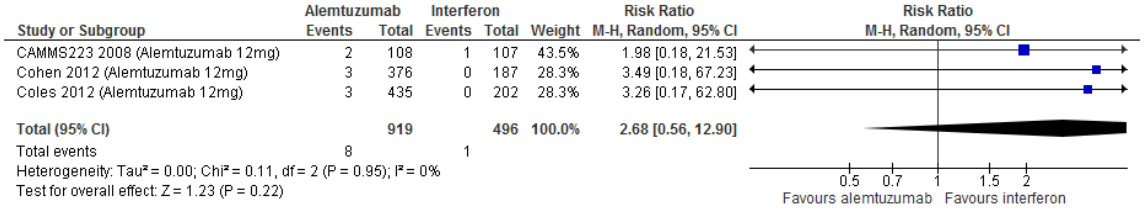


Risk of malignancy – number of participants (104-156 weeks' follow-up)

Risk of infection – number of participants with any infection (104-156 weeks' follow-up)

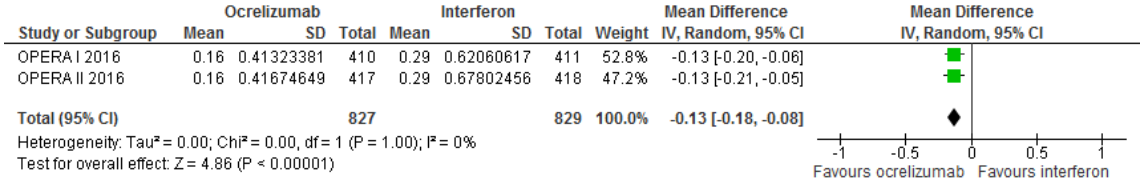


Risk of immune thrombocytopenia purpura – number of participants with any disorder (104-156 weeks' follow-up)

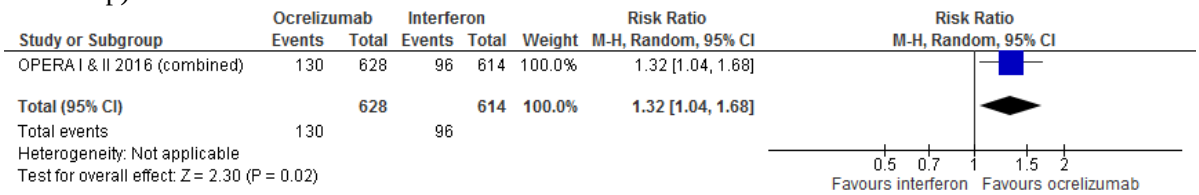


9. Ocrelizumab compared with interferon

Annualised relapse rate (96 weeks' follow-up)

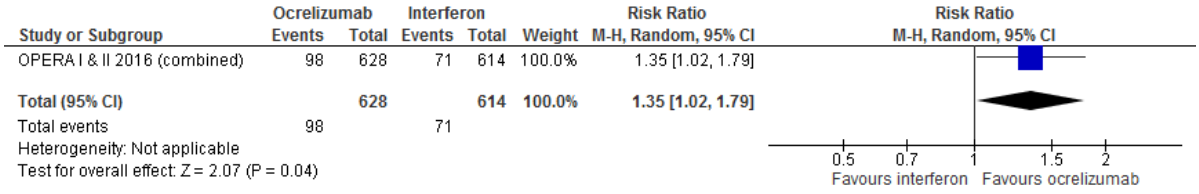


Disability improvement[9] confirmed at 12 weeks – number of participants improved (96 weeks' follow-up)

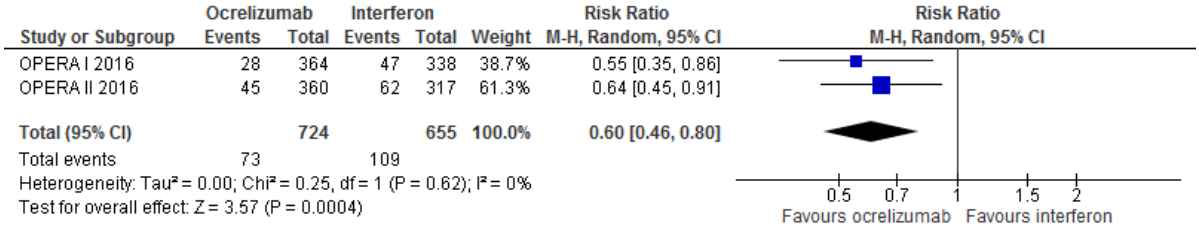


Disability improvement confirmed at 24 weeks – number of participants improved (96 weeks' follow-up)

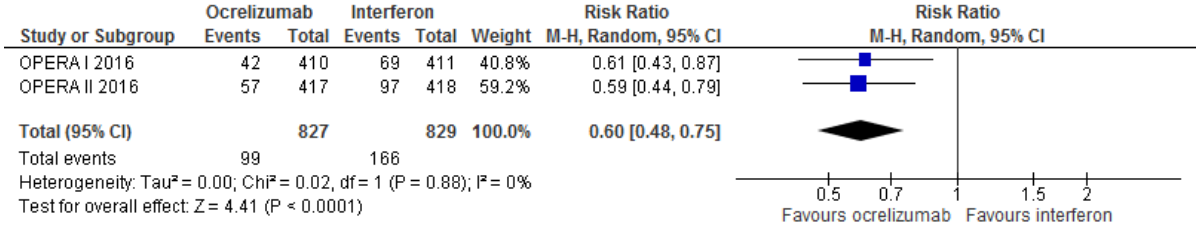
[9] For patients with a baseline EDSS score of ≥2.0 and ≤5.5, disability improvement was defined as a reduction in EDSS score ≥1.0 point compared with baseline EDSS score. For patients with a baseline EDSS score of >5.5, disability improvement was defined as a reduction in EDSS score of ≥0.5 point



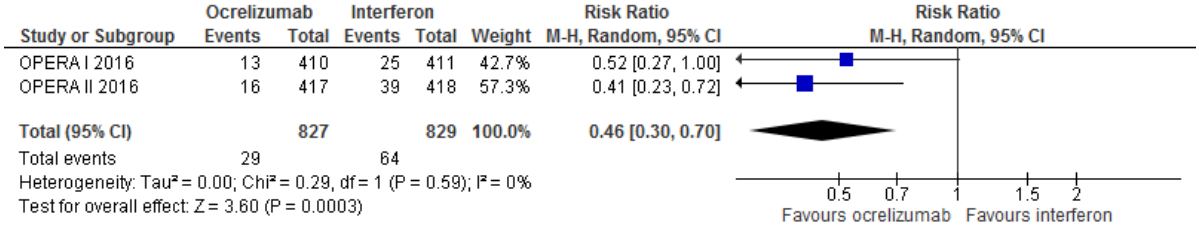
Disability progression[10] - number of participants worsened (96 weeks' follow-up)



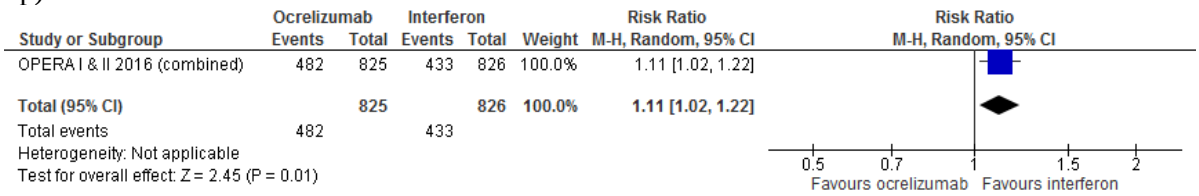
Discontinuation due to any reason (96 weeks' follow-up)



Discontinuation due to side effects (96 weeks' follow-up)

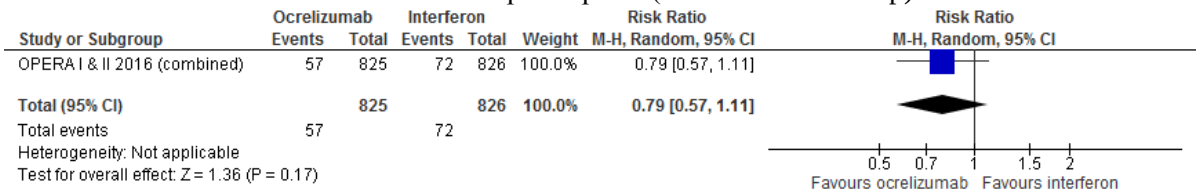


Risk of infection – number of participants with infections and infestations (96 weeks' follow-up)



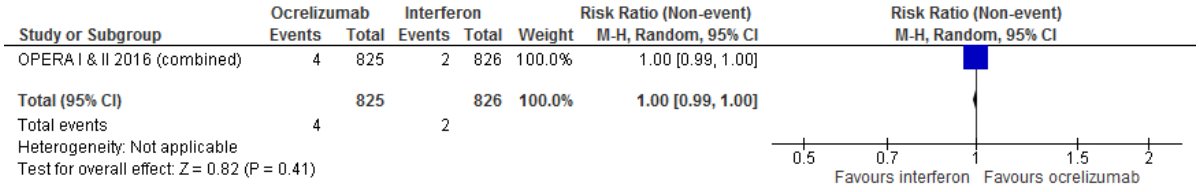
Risk of influenza-like illness

Risk of serious adverse event – number of participants (96 weeks' follow-up)

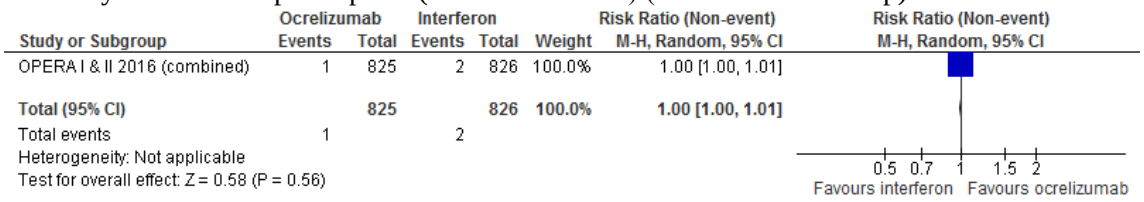


Risk of malignancy – number of participants (risk of non-event) (96 weeks' follow-up)

[10] Disability definitions (EDSS score at Week 96 compared with baseline): worsened, an increase of >0.5;



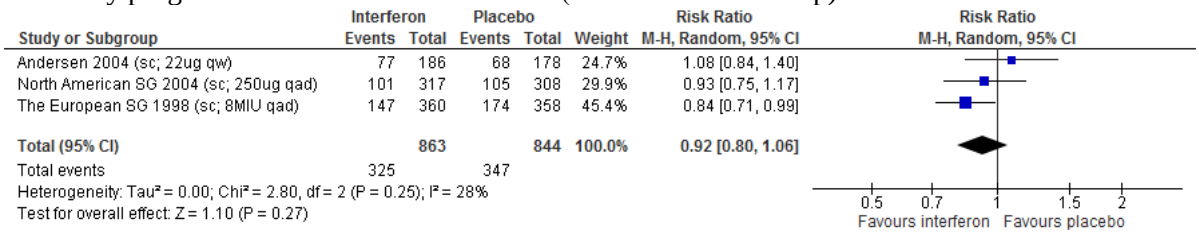
Mortality – number of participants (risk of non-event) (96 weeks' follow-up)



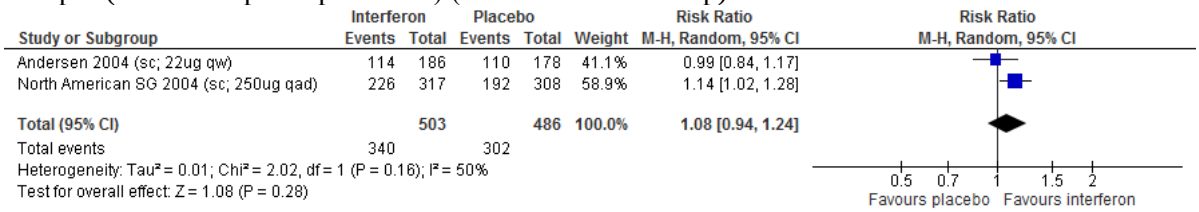
Review question 2_ Secondary progressive MS

1. Interferon compared with placebo

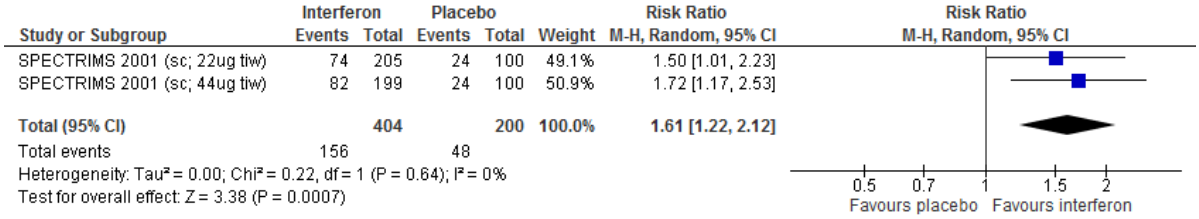
Disability progression[11] confirmed at 6 months (156 weeks' follow-up)



Relapse (number of participants free) (156 weeks' follow-up)



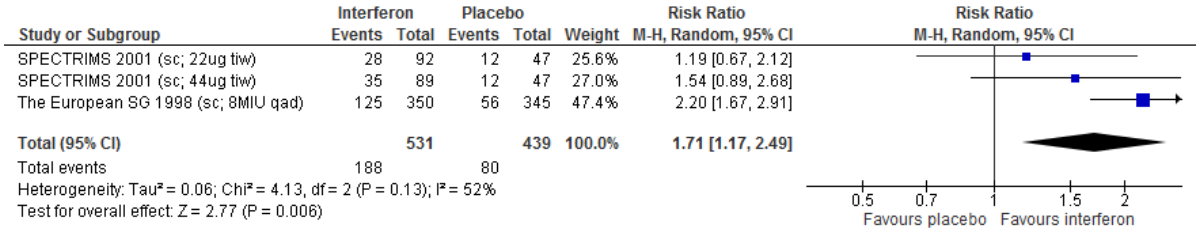
Participants free from new or newly enlarging T2 lesions (156 weeks' follow-up)



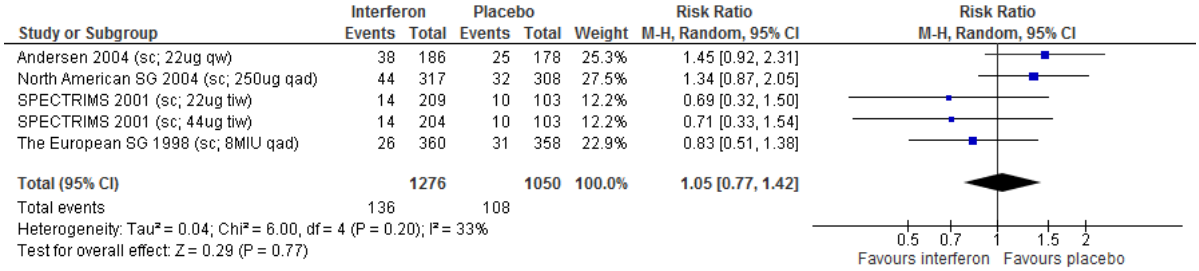
Participants free from combined unique activity (156 weeks' follow-up)

[11] Andersen 2004: defined as an increase from baseline by at least 1.0 point (or 0.5 points if the baseline EDSS score was 5.5 or higher) and confirmed at two consecutive scheduled visits separated by 6 months.

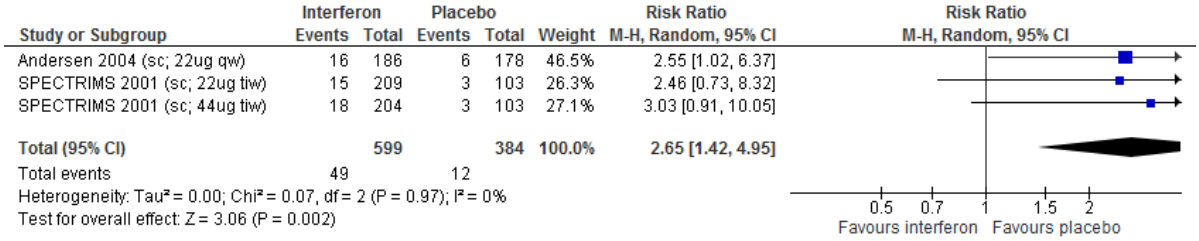
North American Study Group 2004 and The European Study Group: defined as a 1.0 point from the baseline EDSS score (0.5 points if the baseline EDSS score was 6.0 to 6.5) confirmed at two consecutive scheduled examinations spanning 6 months from the onset of progression.



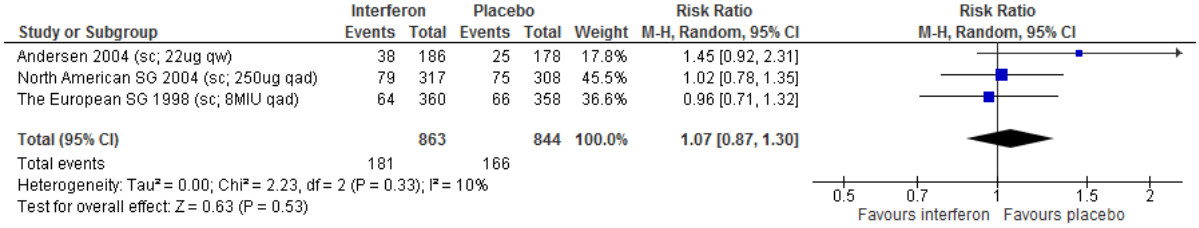
Discontinuation due to any reason (156 weeks' follow-up)



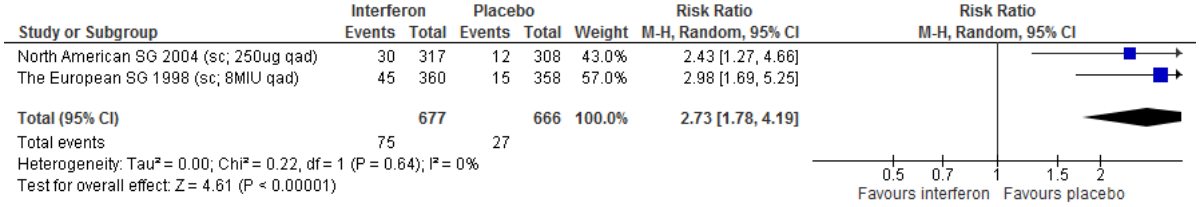
Discontinuation due to side effects (156 weeks' follow-up)



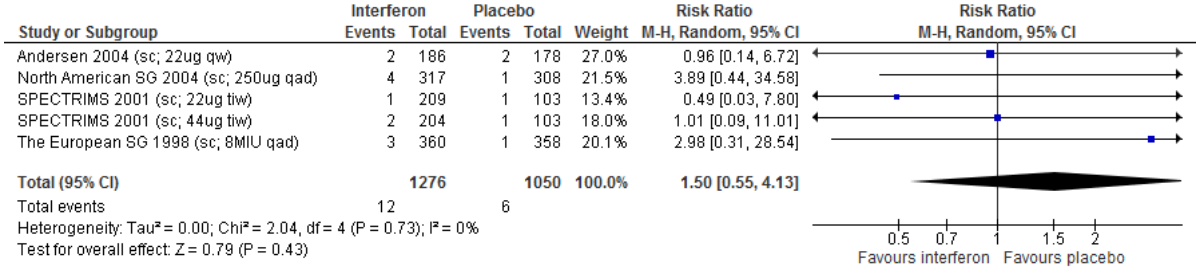
Discontinuation of study drug due to any reason (156 weeks' follow-up)



Discontinuation of study drug due to side effects (156 weeks' follow-up)



Mortality (risk of non-event) (156 weeks' follow-up)



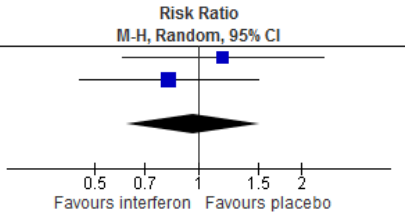
Review question 3

1. Interferon compared with placebo for primary progressive multiple sclerosis

Disability progression confirmed at three months[12] – number of participants worsened (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	8	15	9	20	44.4%	1.19 [0.60, 2.33]
Montalban 2004 (IFNb1b sc; 8 MIU)	12	36	15	37	55.6%	0.82 [0.45, 1.51]
Total (95% CI)		**51**		**57**	**100.0%**	**0.97 [0.62, 1.52]**
Total events	20		24			

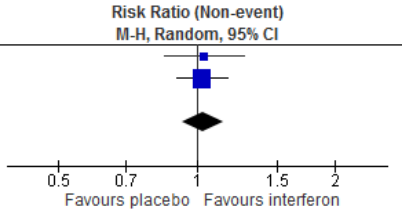
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)



Discontinuation of study drug due to any reason (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	1	15	2	20	28.0%	1.04 [0.85, 1.27]
Montalban 2004 (IFNb1b sc; 8 MIU)	2	36	3	37	72.0%	1.03 [0.91, 1.16]
Total (95% CI)		**51**		**57**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	3		5			

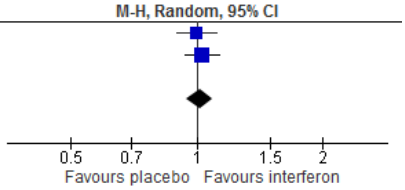
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)



Discontinuation of study drug due to any reason (risk of non-event) (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	0	15	0	20	42.4%	1.00 [0.90, 1.12]
Montalban 2004 (IFNb1b sc; 8 MIU)	1	36	2	37	57.6%	1.03 [0.93, 1.13]
Total (95% CI)		**51**		**57**	**100.0%**	**1.02 [0.95, 1.09]**
Total events	1		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)



[12] Leary 2003: Disability progression defined as a 1.0 point increase in EDSS score for subjects with a baseline EDSS score 5.0, or a 0.5 point increase for subjects with a baseline 5.5. Progression was considered sustained if documented at two consecutive visits 3 months apart; the time of the first visit was recorded as the time to progression.

Montalban 2004: Disability progression defined as ≥1.0 and ≥0.5 point increases on the EDSS for three months in those with baseline scores of ≤5.0 and ≥5.5, respectively.

Appendix 7 _Additional safety data

Question 1

Study ID (original trial) (N†)	Length of exposure	FU*	Discontinuation	Mortality	Side effects
Kappos 2007 (BENEFIT) n=418	Early: 2.96 years (median) Delayed: 1 year (median)	3 yrs	**Due to any reason** Early interferon: 12 **(4.6%)** Delayed interferon: 14 **(8.9%)** **Due to adverse events** Early interferon: 1 **(0.4%)** Delayed interferon: 4 **(2.5%)**	No deaths were reported during the study period.	**Injection site reaction** Early IFN: 158 (54%) Delayed IFN: 68 (39%)
Kappos 2009 (BENEFIT) n=392	Early: 5 years (median) Delayed: 2.9 years (median)	5 yrs	**Due to any reason** Early interferon: 26 **(9.96%)** Delayed interferon: 34 **(21.6%)** **Due to adverse events** Early interferon: 5 **(1.9%)** Delayed interferon: 6 **(3.8%)**	No deaths were reported during the study period.	**Injection site reaction** Early IFN: 164 (56%) Delayed IFN: 71 (40%)
Edan 2014 (BENEFIT) n=284	Early: 7 years (median) Delayed: 4.5 years (median)	8 yrs	Not reported	*"No difference between groups in the total number of patients experiencing ≥1 serious adverse event: 12 patients (6.7%) in the early treatment group and eight patients (7.5%) in the delayed treatment group."*	
Kappos 2016 (BENEFIT)	NR	11 yrs	Not reported	"*The frequency and type of adverse events reported were consistent with the known profile of interferon beta-1b. There were no new safety signals detected at year 11. No serious adverse events were*	

Study ID (original trial) (N†)	Length of exposure	FU*	Discontinuation	Mortality	Side effects
n=278				*reported during BENEFIT 11."*	
REFLEXION (unpublished;NCT00813709) (REFLEX) n=155	NR	5 yrs	***Due to any reason*** Interferon (qw): 20 **(39.2%)** Interferon (tiw): 11 **(23.9%)** Delayed interferon: 20 **(34.5%)** ***Due to adverse events*** Interferon (qw): 4 **(7.8%)** Interferon (tiw): 3 **(6.5%)** Delayed interferon: 5 **(8.6%)**	No deaths were reported during the study period.	**Injection site erythema** Early IFN: 2 (4.35%) Delayed IFN: 4 (6.9%)
Kinkel 2006 (CHAMPS) n=204	NR	5 yrs	*"No new safety concerns with IFN -1a therapy arose during the CHAMPIONS Study"*		
Comi 2013 (PRECISE) n=409	Early: 4.7 years (median) Delayed: 3.5 years (median)	5 yrs	*"GA was well tolerated, with only 71 patient withdrawals (14.8%) over five years due to AEs. AE type, frequency, and severity were consistent with the known safety profile of GA. No significant differences were detected in the incidence of any AE between the early- and delayed-treatment groups. The most common treatment-associated AEs were injection site reactions. Serious AEs were reported in 28 patients in the early-treatment group (including one death during the double-blind phase) and 32 patients in the delayed-treatment group."*		
†Number of participants who started the extension phase, *Number of years follow-up from start of original trial ‡ adjusted for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions volume, and baseline number of Gd+ lesions					

Question 2_Additional safety data

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Kieseier 2015 (ADVANCE) n=1332	Early= 2 years Delayed= 2 years	2 yrs	**Due to any reason** (during extension) PegIFN (2 weeks): 27/438 **(6.2%)** PegIFN (4 weeks): 47/439 **(10.7%)** Delayed pegIFN (2 weeks): 32/228 **(14%)** Delayed pegIFN (4 weeks): 28/227 **(12.3%)** **Due to adverse events** (during extension) PegIFN (2 weeks): 7/438 **(1.6%)** PegIFN (4 weeks): 9/439 **(2%)** Delayed pegIFN (2 weeks): 8/228 **(3.5%)** Delayed pegIFN (4 weeks): 9/227 **(3.96%)**	**Mortality** PegIFN (2 weeks): 3/438 **(0.68%)** PegIFN (4 weeks): 0/439 Delayed pegIFN (2 weeks): 0/228 Delayed pegIFN (4 weeks): 2/227	**Injection site erythema** PegIFN and delayed (2 weeks): 470 **(64%)** PegIFN and delayed (4 weeks): 433 **(59%)**
PRISMS-4 2001 (PRISMS) n=506	NR	4 yrs	**Due to any reason** (during extension) IFN beta-1a (22ug): 28 **(11%)** IFN beta-1a (44ug): 45 **(18%)** Delayed 22ug: 37 **(11%)** Delayed 44ug: 36 **(21%)** **Due to adverse events** (during extension) IFN beta-1a (22ug): 3 **(1.8%)** IFN beta-1a (44ug): 9 **(5.4%)** Delayed 22ug: 3 **(14%)** Delayed 44ug: 12 **(13.8%)**	Adverse events during the extension were similar to those observed in PRISMS-2 (table 4), and most were mild. Fifty-four patients experienced 67 serious adverse events during years 3 and 4, and the incidence of serious adverse events was similar between groups. One patient in the Rx22 group died after a myocardial infarction.	
Kappos 2006 (PRISMS) n=382	NR	7-8	NR	**Mortality** IFN beta-1a (22ug): 5/189 **(2.7%)** IFN beta-1a (44ug): 1/184 **(<1%)** Delayed treatment: 2/187 **(1%)**	NR

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Rudick 2005/ Rudick 2010 (MSCRG) n=172	Early= 4.2 years¥ Delayed= 4.9 years¥	8 yrs	**Due to any reason** (during extension) Early IFN: 32 (27.8%) Delayed IFN: 34 (33%)	NR	NR
Ebers 2010/ Reder 2010 (IFNB MS trial) n=260	The median total length of exposure to IFNB-1b since the start of the pivotal trial was 7.9 years	16 yrs	NR	**Mortality** IFN 250ug vs. placebo: p=0.0049 IFN 50ug vs. placebo: p=0.0402 IFN beta-1b (250ug): 6 (5.4%) IFN beta-1b (50ug): 9 (8.3%) Placebo: 20 (18.4%)	**Injection-site reactions** Interferon beta-1b (250ug): 83 **(86.5%)** Placebo: 33 **(41.8%)**
Goodin 2012 (IFNB MS trial) n=366	NR	21 years	NR	**Mortality** HR=0.53 (0.31-0.9); p=0.017 (IFN 250ug vs. placebo) HR=0.54 (0.32-0.91); p=0.0202 (IFN 50ug vs. placebo) IFN beta-1b (250ug): 22 **(18%)** IFN beta-1b (50ug): 22 **(17.9%)** Placebo: 37 **(30.6%)**	NR
Johnson 2000 (Johnson 1995)	Early= 5.8 years Delayed= NR	6 yrs	**Due to any reason** (during open-label phase) Early treatment: 24 **(23.8%)**	NR	**Injection-site reactions** (during open-label phase) Early treatment: 2.4%

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
n=208			Delayed treatment: 32 **(30%)**		Delayed treatment: 0.9%
Gold 2016 (DEFINE and CONFIRM) n=1736	NR	5 yrs	Rates of discontinuation due to individual AEs in were low (≤2% for individual AEs in each treatment group).	**Mortality** Dimethyl fumarate (BID): 2 /501 **(<1%)** PBO/BID: 1/249 **(<1%)** GA/BID: 0/118 **(0%)**	**Infections** Dimethyl fumarate (BID): 327/501 **(65%)** PBO/BID: 141/249 **(57%)** GA/BID: 61/118 **(52%)** **Malignancies** Dimethyl fumarate (BID): 10/501 **(2%)** PBO/BID: 5/249 **(2%)** GA/BID: 0/118 **(0%)** **Progressive multifocal leukoencephalopathy*** Dimethyl fumarate (BID): 0/501 PBO/BID: 0/249 GA/BID: 0/118
O'Conner 2016 (TEMSO) n=742	T (14mg) = 6.2 years (median) T (7mg) = 5.7 years (median) Delayed (14mg) = 3.8 years	Up to 9 yrs	**Due to adverse events** Teriflunomide 14mg: 24 **(9.6%)** Delayed teriflunomide 14mg: 11 **(10.4%)**	**Adverse events leading to death** Teriflunomide 14mg: 1 **(<1%)** Delayed teriflunomide 14mg: 0 **(0%)**	**Serious adverse events** Teriflunomide 14mg: 55 **(22%)** Delayed teriflunomide 14mg: 19 **(17.9%)** *Peripheral neuropathy confirmed via electrophysical nerve conduction tests*

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
	(median) Delayed (7mg) = 3.7 years (median)				*was reported for 9 patients receiving teriflunomide 14 mg (1 of whom had 2 events) and 5 patients receiving 7 mg.*
Kappos 2015 (FREEDOMS) n=920	Fingolimod 0.5mg= 3.8 years Fingolimod 1.25mg= 3.8 years Delayed= 1.8 years	4-6 yrs	**Due to any reason** (during extension) Early (0.5mg): 41 **(12.4%)** Delayed treatment (0.5mg): 29 **(18.7%)** **Due to adverse event** (including abnormal laboratory values) Early (0.5mg): 15 **(4.5%)** Delayed treatment (0.5mg): 16 **(10.3%)**	NA	**Infections** Fingolimod (0.5mg): 240 **(72.5%)** Fingolimod (1.25mg): 204 **(70.6%)** Delayed treatment: 209 **(69.7%)** **Serious adverse events** Fingolimod (0.5mg): 31 **(9.4%)** Fingolimod (1.25mg): 31 (10.7%) Delayed treatment: 28 **(9.3%)** **Neoplasms** Fingolimod (0.5mg): 7 **(2.1%)** Fingolimod (1.25mg): 5 **(1.7%)** Delayed treatment: 5 **(1.67%)** **Herpesvirus infection** Fingolimod (0.5mg): 40 **(12.1%)** Fingolimod (1.25mg): 31 **(10.7%)** Delayed treatment: 28 **(9.3%)** **Bradyarrhythmia** Fingolimod (0.5mg): 0 **(0%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 0 **(0%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Bradycardia Fingolimod (0.5mg): 1 **(0.3%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 3 **(1%)** **Macular edema** Fingolimod (0.5mg): 1 **(0.3%)** Fingolimod (1.25mg): 1 **(0.4%)** Delayed treatment: 1 **(0.3%)**
NCT00355134 (unpublished) (FREEDOMS II) n=632	NR	4.5 yrs	**Due to any reason** (during extension) Fingolimod (0.5mg): 37 **(17%)** Fingolimod (1.25mg): 31 **(15.3%)** Delayed treatment: 35 **(16.5%)** **Due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 11 **(5%)** Fingolimod (1.25mg): 17 **(8.4%)** Delayed treatment: 12 **(5.7%)**	NA	Reported only for whole group only
Khatri 2011 (TRANSFORMS) n=1027	Early= 2 years Delayed= 1 year	2 yrs	**Of study drug due to any reason** Fingolimod (0.5mg): 38 **(10.7%)** Delayed fingolimod (0.5mg): 28 **(16.7%)** **Of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 21 **(5.9%)** Delayed fingolimod (0.5mg): 9 **(5.4%)**		**Infectious adverse events (during extension)** Fingolimod (0.5mg): 204 **(47.6%)** Delayed fingolimod (0.5mg): 91 **(54%)** **Serious adverse event (during extension)** Fingolimod (0.5mg): 19 **(4.4%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Delayed fingolimod (0.5mg): 8 **(5%)** **Neoplasms (during extension)** (benign, malignant, unspecified including cysts and polyps) Fingolimod (0.5mg): 6 (**1.4%)** Delayed fingolimod (0.5mg): 0 (**0%)** **Herpes zoster (during extension) (disseminated and ophthalmic)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)** **Bradycardia (during extension)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)** **Macular oedema (during extension)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 (**0.06%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
Cohen 2015 (TRANSFORMS) n=1027	NR	4.5 yrs	**Of study drug due to any reason** Fingolimod (0.5mg): 75 **(21.1%)** Delayed fingolimod (0.5mg): 44 **(26%)** **Of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 35 **(9.8%)** Delayed fingolimod (0.5mg): 11 **(6.6%)**		**Malignancies** (basal cell carcinoma, breast cancer) Fingolimod (0.5mg): 8/356 (2.24%) Delayed fingolimod (0.5mg): 1/167 (0.6%) **Serious adverse events** Fingolimod (0.5mg): 55 (**15.4%)** Delayed fingolimod (0.5mg): 21 **(12.6%)** **Herpes viral infection** Fingolimod (0.5mg): 36 **(10.1%)** Delayed fingolimod (0.5mg): 25 **(15%)** **Herpes zoster (disseminated)** Fingolimod (0.5mg): 0 **(0%)** Delayed fingolimod (0.5mg): 1 **(0.23%)**
Giovannoni 2014 (SELECT) n=517	Early= 2 years Delayed= 1 year	2 yrs	**Of study drug due to any reason** (during open-label phase) Daclizumab (150mg): 27 **(15.7%)** Delayed treatment: 20 **(11.8%)** **Of study drug due to adverse events** (during open-label phase) Daclizumab (150mg): 9 **(5.2%)** Delayed treatment: 3 **(1.8%)**	**Mortality** One patient in the washout and re-initiation group died because of autoimmune hepatitis after re-initiation of 300 mg daclizumab HYP. A contributory role of daclizumab HYP could not be excluded.	**Autoimmune disorders** (autoimmune hepatitis, Grave's disease or hyperthyroidism, ulcerative colitis) Continuous treatment: 3/173 **(1.7%)** Washout and re-initiation: 1/174 **(<1%)** Delayed treatment: 0/170 **(0%)**

Study ID (original trial) N†	Length of exposure‡	FU*	Discontinuation	Mortality	Side effects
					Malignancy Continuous treatment: 0/173 **(0%)** Washout and re-initiation: 0/174 **(0%)** Delayed treatment: 1/170 **(<1%)** **Serious Infections** Continuous treatment: 4/173 **(2.3%)** Washout and re-initiation: 4/174 **(2.4%)** Delayed treatment: 5/170 **(2.9%)** **Serious cutaneous events** Continuous treatment: 3/173 **(1.73%)** Washout and re-initiation: 1/174 **(0.57%)** Delayed treatment: 2/170 **(1.17%)**

‡Mean number of years on study drug
¥Combined interferon beta-1a and interferon beta-1b
*Subsequent to the data cutoff for this report, a fatal case of progressive multifocal leukoencephalopathy (PML) in a patient treated with DMF 240 mg TID was reported in the setting of severe, prolonged lymphopenia (~290–580 cells/mL3 over 3.5 years)

Study ID (original trial) (N†)	FU*	Discontinuation	Mortality	Side effects
Giovannoni 2010 (CLARITY) n=1326	3 yrs	**Due to any reason** Cladribine 3.5mg: 35 **(8.1%)** Cladribine 5.25mg: 50 **(11%)** Placebo: 57 **(13%)** **Due to adverse events** Cladribine 3.5mg: 5 **(1.1%)** Cladribine 5.25mg: 9 **(2%)** Placebo: 5 **(1.1%)**	Cladribine 3.5mg: 2 **(0.46%)** Cladribine 5.25mg: 2 **(0.44%)** Placebo: 0 **(0%)**	**Any serious adverse event** Cladribine 3.5mg: 36 **(8.4%)** Cladribine 5.25mg: 41 **(9%)** Placebo: 28 **(6.4%)** **Infections or infestations (number of participants with any)** Cladribine 3.5mg: 205 **(47.7%)** Cladribine 5.25mg: 222 **(48.9%)** Placebo: 185 **(42.5%)** **Serious infections or infestations (number of participants with any)** Cladribine 3.5mg: 10 **(2.3%)** Cladribine 5.25mg: 13 **(2.9%)** Placebo: 7 **(1.6%)** **Neoplasms (number of participants with any)** Cladribine 3.5mg: 6 **(1.4%)** Cladribine 5.25mg: 4 **(0.9%)** Placebo: 0 **(0%)**

Appendix 8_ Results of extension studies

Table 1: Results of extension studies comparing early and delayed treatment with interferon in CIS

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
	Findings favouring early treatment	**Findings indicating no between group differences (or descriptive results)**	**Findings favouring early treatment**	**Findings indicating no between group differences (or descriptive results)**	**Findings favouring delayed treatment**	**Findings indicating no between group differences**
Kappos 2007	**Conversion to CDMS** HR=0.59; 95% CI, 0.44-0.80; p=0.0011 RR= 0.70; 95% CI, 0.56-0.88; p=0.002 Early treatment: 99/292 (34%) Delayed treatment: 85/176 (48%) **EDSS Progression** HR= 0.60; 95% CI, 0.39-0.92; p=0.022 RR= 0.63; 95% CI, 0.43-0.94; p=0.02 Early treatment: 42/292 (14%) Delayed treatment: 40/176 (23%)		**Cumulative number of newly active lesions** Fewer newly active lesions developed in the early treatment group over 3 years than in the delayed treatment group (p<0·0001).	**Absolute change in T2 lesion volume** No significant difference between groups (p=0·070) **Change in brain volume (%)** No significant difference between groups (p=0.15)	**Injection site reaction** RR=1.38, 95% CI, 1.11-1.71, p=0.003 158 (54%) patients in the early group 68 (39%) patients in the delayed group **Leucopenia** RR=1.69, 95% CI, 1.08-2.64, p=0.003 65 (22%) patients in the early group 22 (13%) patients in the delayed group **Raised alanine aminostransferase concentrations** RR=2.28, 95% CI, 1.25-4.19, p=0.008 46 (16%) patients in the early group 12 (7%) in the delayed group	**Flu-like symptoms** RR=1.00, 95% CI, 0.82-1.21, p=0.97 144 (49%) patients in the early group 86 (49%) patients in the delayed group

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
Kappos 2009	**Conversion to CDMS** HR=0.63; 95% CI, 0.48-0.83; p=0.003 RR= 0.70; 95% CI, 0.56-0.88; p=0.002 Early treatment: 124/292 (42%) Delayed treatment: 94/176 (53%)	**EDSS Progression** HR= 0.76; 95% CI, 0.50-1.17; p=0.177 RR=0.83; 95% CI, 0.60-1.15; p=0.27 Early treatment: 65/292 (22%) Delayed treatment: 47/176 (27%)	**Cumulative number of newly active lesions** Early treatment group: 9.7, 14.7 (mean, SD) Delayed group: 12.9, 15.7 (mean, SD) Significant when authors controlled for baseline scores, p=0.006	**Absolute change in T2 lesion volume** Early treatment group: -0.6, 4.1 (mean, SD) Delayed group: -0.3, 2.4 (mean, SD) **Change in brain volume (%)** Early treatment group: -2.7, 2.4 (mean, SD) Delayed group: -2.0, 2.1 (mean, SD) Not significant when authors controlled for baseline scores, p=0.121	**Injection site reaction** RR=1.39, 95% CI, 1.13-1.71, p=0.002 164 (56%) patients in the early group 71 (40%) patients in the delayed group **Leucopenia** RR=1.69, 95% CI, 1.13-2.54, p=0.01 73 (25%) patients in the early group 26 (15%) patients in the delayed group	**Flu-like syndrome complex** RR=1.05, 95% CI, 0.88-1.25, p=0.97 158 (54%) patients in the early group 91 (52%) patients in the delayed group
Edan 2014	**Conversion to CDMS** HR=0.678; 95% CI, 0.525-0.875; p=0.003 Early treatment: 55.5% Delayed treatment: 65.8%	**EDSS Progression** RR=1.19; 95% CI, 0.83-1.72; p=0.35 Early treatment: 60/178 (34%) Delayed treatment: 30/106 (28%)				*The authors reported no difference between groups in the total number of patients experiencing ≥1 serious adverse event: 12 patients (6.7%) in the early treatment group and eight patients (7.5%) in the delayed treatment group.*
REFLEXION (NCT00813709)	**Conversion to CDMS** Interferon tiw vs delayed - HR=0.56, 95% CI, 0.38-0.82, p=0.002 Interferon qw vs delayed - HR=0.57, 95% CI, 0.39-0.84, p=0.006 **Percentage of Relapse-Free**			**Percent Change From Baseline in Brain Volume**** Interferon (qw): -0.86 (1.073), mean (SD) Interferon (tiw): -1.14 (1.321), mean (SD) Delayed interferon: -1.02 (1.248), mean (SD)		

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
	Participants Interferon (qw): 102/175 (58.3%) Interferon (tiw): 88/171 (51.5%) Delayed interferon: 73/171 (42.7%)			**Number of new T2 Lesions**** Interferon (qw): 1.39 (2.573), mean (SD) Interferon (tiw): 1.19 (4.217), mean (SD) Delayed interferon: 0.83 (1.545), mean (SD) **Number of new gadolinium enhanced (Gd+) Lesions**** Interferon (qw): 0.40 (1.354), mean (SD) Interferon (tiw): 0.41 (1.754), mean (SD) Delayed interferon: 0.17 (0.506), mean (SD)		
REFLEXION (NCT00813709)	**Percentage of Relapse-Free Participants** Interferon (qw): 79/175 (45.1%) Interferon (tiw): 70/171 (40.9%) Delayed interferon: 59/171 (34.5%)	**Conversion to CDMS**** (cumulative % of participants with CMDS) Interferon (qw): 40.7%, 95% CI, 32.8 to 48.6 Interferon (tiw): 39.2%, 95% CI, 30.8 to 47.6 Delayed interferon: 44.6%, 95% CI, 36.6 to 52.6		**Percent Change From Baseline in Brain Volume**** Interferon (qw): -0.86 (1.073), mean (SD) Interferon (tiw): -1.14 (1.321), mean (SD) Delayed interferon: -1.02 (1.248), mean (SD) **Number of new T2 Lesions**** Interferon (qw): 1.17 (2.628), mean (SD) Interferon (tiw): 1.35 (3.284), mean (SD) Delayed interferon: 1.17 (2.576), mean (SD)		**Discontinuation due to any reason**** Interferon (qw): 20/51 (39.2%) Interferon (tiw): 11/46 (23.9%) Delayed interferon: 20/58 (34.5%) **Discontinuation due to adverse events**** Interferon (qw): 4/51 (7.8%) Interferon (tiw): 3/46 (6.5%) Delayed interferon: 5/58 (8.6%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
				Number of new gadolinium enhanced (Gd+) Lesions** Interferon (qw): 0.36 (1.225), mean (SD) Interferon (tiw): 0.48 (1.618), mean (SD) Delayed interferon: 0.24 (0.823), mean (SD)		
Kinkel 2006	**Conversion to CDMS** HR= 0.65, 95% CI, 0.43-0.97; p=0.03 (unadjusted) HR= 0.57, 95% CI, 0.38-0.86; p=0.008 (adjusted for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions volume, and baseline number of Gd+ lesions)			**New or enlarging T2 lesions** Early treatment: 3.5 (0.5-8.5); median (IQR) Delayed treatment: 6.0 (2-13); median (IQR) Wilcoxon rank sum test indicated no significant difference (p=0.05), as the 0.01 level of significance was not met. **Gad lesions (% of participants with ≥1 lesion)** Early treatment: 29% Delayed treatment: 30% Wilcoxon rank sum test indicated no significant difference between groups (p=0.81) **Change in T2 lesions volume (mm3)** Early treatment: 646 (-105, 2,599); median (IQR) Delayed treatment: 827 (107, 4,112); median (IQR) Wilcoxon rank sum test		*"No new safety concerns with IFN -1a therapy arose during the CHAMPIONS Study."*

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety	
				indicated no significant difference between groups (p=0.10)		
Comi 2013	**<u>Conversion to CDMS</u>** HR= 0.59, 95% CI, 0.44-0.86; p=0.008 (adjusted baseline values) Early treatment: 55/163 (34%) Delayed treatment: 71/126 (56%)		**<u>Cumulative number of T2 lesions per year</u>** Early treatment group: 1.74, 2.67 (mean, SD) Delayed group: 2.99, 4.36 (mean, SD) **<u>Cumulative number of new GAD lesions per year</u>** Early treatment group: 0.68, 1.41 (mean, SD) Delayed group: 1.45, 2.76 (mean, SD) **<u>Percent brain volume change from baseline to last observed value</u>** Early treatment group: -0.99, 1.27 (mean, SD) Delayed group: -1.28, 1.31 (mean, SD)			*Aurthors reported that GA was well tolerated, with only 71 patient withdrawals (14.8%) over five years due to AEs. AE type, frequency, and severity were consistent with the known safety profile of GA. No significant differences were detected in the incidence of any AE between the early- and delayed-treatment groups. The most common treatment-associated AEs were injection site reactions. Serious AEs were reported in 28 patients in the early-treatment group (including one death during the double-blind phase) and 32 patients in the delayed-treatment group.*

*From trial baseline

†Proportion of original cohort who completed the extension phase

¥Actual N not reported, baseline N used

**No statistical analysis reported

HR= Hazard ratio

RR= relative risk

CI= confidence intervals

FAMS-TOI= Funtional Assessment of multiple sclerosis
SMD= Standard mean difference
CDMS = Clinically Definite Multiple Sclerosis

Table 2: Results of extension studies comparing early and delayed treatment with interferon in RRMS

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	Findings favouring early treatment	Findings indicating no between group differences (or descriptive results)	Findings favouring early treatment	Findings indicating no between group differences (or descriptive results)	Findings favouring early treatment	Findings favouring delayed treatment	Findings indicating no between group differences
Kieseier 2015 1332 (88%)	**<u>Annualised relapse rate</u>** RR¥= 0.629; 95% CI, 0.50-0.79; p<0.0001 Peginterferon (2 weeks): 0.22; 95% CI, 0.183-0.267 Delayed treatment: 0.351, 95% CI, 0.295-0.418 **<u>Disability progression</u>** (24 week confirmed) RR= 0.58; 95% CI, 0.39-0.87, p=0.009 Peginterferon (2 weeks): 34/512 (6.6%) Delayed treatment: 57/500 (11.4%)	**<u>Annualised relapse rate</u>** RR¥= 0.829; 95% CI, 0.666-1.030; p=0.0906 Peginterferon (4 weeks): 0.291, 95% CI, 0.244-0.348 Delayed treatment: 0.351, 95% CI, 0.295-0.418 **<u>Disability progression</u>** RR= 0.91; 95% CI, 0.64-1.30, p=0.61 Peginterferon (4 weeks): 52/500 (10.4%) Delayed treatment: 57/500 (11.4%)	**<u>New or newly enlarging T2-weighted hyperintense lesions at 2 years</u>** Lesion mean ratio: 0.84, 95% CI, 0.69-1.03, p=0.0973[β] Peginterferon (4 weeks): 12.5 (adjusted mean number of lesions) Delayed treatment: 14.8 (adjusted mean number of lesions) **<u>Gd+ lesions at 2 years</u>** p=0.2169[δ] Peginterferon (2 weeks): 0.7 (0.12), mean (SE) Delayed treatment: 0.5	**<u>New or newly enlarging T2-weighted hyperintense lesions at 2 years</u>** Lesion mean ratio: 0.84, 95% CI, 0.69-1.03, p=0.0973[β] Peginterferon (4 weeks): 12.5 (adjusted mean number of lesions) Delayed treatment: 14.8 (adjusted mean number of lesions) **<u>Gd+ lesions at 2 years</u>** p=0.2169[δ] Peginterferon (2 weeks): 0.7 (0.12), mean (SE) Delayed treatment: 0.5			**<u>Mortality</u>** Peginterferon (2 weeks): 3/438 Peginterferon (4 weeks): 0/439 Delayed peginterferon (2 weeks): 0/228 Delayed peginterferon (4 weeks): 2/227 **<u>Serious adverse events</u>** Peginterferon (2 weeks): 56/438 (13%) Peginterferon (4 weeks): 62/439 (14%) Delayed peginterferon (2 weeks): 39/228 (17%) Delayed peginterferon (4 weeks): 34/227 (15%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
			(0.08), mean (SE)	(0.08), mean (SE)			
Gold 2016		**Annualised relapse rate** (cumulative from baseline to year 5)** BID/BID: 0.163; 95% CI, 0.14-19 PBO/BID: 0.24; 95% CI, 0.196-0.296 GA/BID: 0.199; 95% CI, 0.148, 0.269 **Disability progression** (proportion progressed at 5 years, confirmed at 24 weeks)** BID/BID: 18.6%; 95% CI, 15.3%-22.4% TID/TID: 21.4% PBO/BID: 21.1%; 95% CI, 16.2%-22.4% PBO/TID: 26% GA/BID: 25.7%; 95% CI, 18.4%-35.2% GA/TID: 20.3%		**Brain atrophy** (only 23% of participants entering ENDORSE included in MRI analyses presented here) BID/BID (N=129): -0.85 (0.958), mean (SD) PBO/DMF (N=103): -1.19 (1.252), mean (SD) GA/DMF (N=57): -1.07 (1.272), mean (SD) Authors report that adjusted percent brain volume change from baseline was not significantly different in BID/BID compared with PBO/DMF (p=0.168) or GA/DMF (p=0.500)		**Mortality** BID/BID: 2/501 (<1%) TID/TID: 2/501 (<1%) PBO/BID: 1/249 (<1%) PBO/TID: 0/248 (0%) GA/BID: 0/118 (0%) GA/TID: 0/119 (0%) **Malignancies**** BID/BID: 10/501 (2%) TID/TID: 8/501 (2%) PBO/BID: 5/249 (2%) PBO/TID: 0/248 (0%) GA/BID: 0/118 (0%) GA/TID: 3/119 (3%)	**Infections**** BID/BID: 327/501 (65%) TID/TID: 322/501 (64%) PBO/BID: 141/249 (57%) PBO/TID: 139/248 (56%) GA/BID: 61/118 (52%) GA/TID: 55/119 (46%) **Serious infections**** BID/BID: 18/501 (4%) TID/TID: 13/501 (3%) PBO/BID: 8/249 (3%) PBO/TID: 7/248 (3%) GA/BID: 2/118 (2%) GA/TID: 4/119 (3%)
Kappos 2015	**Annualised relapse rate** Fingolimod (0.5mg) vs delayed treatment - ARR ratio= 0.52; 95 % CI, 0.42-0.64; p<0.0001¤ Fingolimod (1.25mg) vs delayed treatment -		**New or newly enlarging T2-weighted hyperintense lesions at 2 years‡** Fingolimod (0.5mg) vs delayed treatment - p<0.0001 Fingolimod (1.25mg) vs delayed treatment -				**Infections** Fingolimod (0.5mg): 240/331 (72.5%) Fingolimod (1.25mg): 204/289 (70.6%) Delayed treatment: 209/300 (69.7%) **Serious adverse events**

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	ARR ratio= 0.46; 95 % CI, 0.37-0.57; p<0.0001¤ Fingolimod (0.5mg): 0.19; 95% CI, 0.16-0.22 Fingolimod (1.25mg): 0.16; 95% CI, 0.14-0.20 Delayed treatment: 0.36; 95% CI, 0.31-0.41 **Disability progression** (12 week confirmed)Δ Fingolimod (0.5mg) vs delayed treatment - p<0.0171 Fingolimod (1.25mg) vs delayed treatment - p<0.0165 Fingolimod (0.5mg): 73.9%; 95% CI, 69.4%-78.4% Fingolimod (1.25mg): 74.2%; 95% CI, 69.5-79.8% Delayed treatment: 66.3%; 95% CI, 61.3%-71.3%		p<0.0001 Fingolimod (0.5mg): 4.5; 95% CI, 4.27-4.68 Fingolimod (1.25mg): 4.0; 95% CI, 3.80-4.21 Delayed treatment: 11.0; 95% CI, 10.68-11.36 **Gd+ lesions at 2 years**Æ Fingolimod (0.5mg) vs delayed treatment - p<0.0001 Fingolimod (1.25mg) vs delayed treatment - p<0.0001 Fingolimod (0.5mg): 1.1; 95% CI, 0.98-1.23 Fingolimod (1.25mg): 0.8; 95% CI, 0.70-0.94 Delayed treatment: 3.7; 95% CI, 3.42-3.91 **Percent brain volume change**ð Fingolimod (0.5mg) vs delayed treatment - p<0.0013 Fingolimod (1.25mg) vs delayed treatment - p<0.0010 Fingolimod (0.5mg): -1.7; 95% CI, -1.91, -1.43 Fingolimod (1.25mg): -				Fingolimod (0.5mg): 31/331 (9.4%) Fingolimod (1.25mg): 31/289 (10.7%) Delayed treatment: 28/300 (9.3%) **Neoplasms** Fingolimod (0.5mg): 7/331 (2.1%) Fingolimod (1.25mg): 5/289 (1.7%) Delayed treatment: 5/300 (1.67%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
			1.6; 95% CI, -1.88, -1.40 Delayed treatment: -2.2; 95% CI, -2.51, -1.97				
NCT00355134 (unpublished)	**Aggregate Annualized Relapse Rate (ARR)** (trial baseline until end of extension, up to approximately 54 months) Fingolimod (0.5mg): 0.19, 95% CI, 0.157-0.234 Fingolimod (1.25mg): 0.18, 95% CI, 0.147-0.222 Delayed treatment: 0.36, 95% CI, 0.305-0.431 **Percentage of Participants Relapse-free*** (trial baseline until end of extension, up to approximately 54 months) Fingolimod (0.5mg): 66.57%, 95% CI, 60.86-72.28 Fingolimod (1.25mg): 63.88%; 95% CI, 56.19-71.57 Delayed treatment: 49.12% , 95% CI, 43.35-54.89			**Number of New or Newly Enlarged T2 Lesions** (from month 24 to 36; N=319) Fingolimod (0.5mg): 0.45 (1.360), mean (SD) Fingolimod (1.25mg): 0.63 (2.856), mean (SD) Delayed treatment: 0.63 (1.455), mean (SD) **Number of Gadolinium-enhanced T1 Lesions** (during extension study, up to approximately 54 months; N=562) Fingolimod (0.5mg): 0.09 (0.308), mean (SD) Fingolimod (1.25mg): 0.46 (2.381), mean (SD) Delayed treatment: 0.45 (3.618), mean (SD) **Percent Change From Baseline in Brain Volume** (during extension study, up to approximately 54			**Discontinuation due to any reason** (during extension) Fingolimod (0.5mg): 37/217 (17%) Fingolimod (1.25mg): 31/203 (15.3%) Delayed treatment: 35/212 (16.5%) **Discontinuation due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 11/217 (5%) Fingolimod (1.25mg): 17/203 (8.4%) Delayed treatment: 12/212 (5.7%%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	*generated from Kaplan-Meier curves of the time to first relapse			months; N=547) Fingolimod (0.5mg): -1.27% (1.69), mean (SD) Fingolimod (1.25mg): -1.13% (1.64), mean (SD) Delayed treatment: -1.69% (1.96) , mean (SD)			
PRISMS-4 506 (90%)	**Annualised relapse rate** (relapse count/year) *Years 1-4* RR=0.70, 0.59-0.82; p<0.001 (44ug) RR=0.76, 0.66-0.89; p<0.001 (22ug) *Years 3-4* RR=0.73, 0.58-0.94; p=0.014 (44ug) RR=1.01, 0.80-1.28; p=0.946 (22ug) **Proportion of participants relapse free** Interferon beta-1a (22ug): 14.4% (p=0.02) Interferon beta-1a (44ug): 19% (p<0.001) Delayed treatment: 6.7%	**Disability progression** (number of participants free from) Interferon beta-1a (22ug): 88/173 (51%) - ns Interferon beta-1a (44ug): 92/164 (54.3%) - ns Delayed treatment: 74/161 (46%)	**New T2 lesions per patient per scan** *Years 1-4* Interferon beta-1a (22ug): 1.3 (1-1.75) (p<0.001) Interferon beta-1a (44ug): 0.5 (0.33-0.67) (p<0.001) Delayed 22ug: 2 (1.67-3.25) Delayed 44ug: 2.7 (2-3.5) *Years 3-4* Interferon beta-1a (22ug): 1 (0.5-1) (p<0.001) Interferon beta-1a (44ug): 0 (0-0 (p<0.001) Delayed 22ug: 0.5 (0.5-1) Delayed 44ug: 1 (0.5-1.5)				**Discontinuation due to any reason during extension** Interferon beta-1a (22ug): 28/251 (11%) Interferon beta-1a (44ug): 45/251 (18%) Delayed 22ug: 37/331 (11%) Delayed 44ug: 36/171 (21%) *(excluding patients who took no drug in years 3 and 4)*

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
Kappos 2006	**Disability progression** (confirmed at 3 months; 4 years' follow-up) *Participants with missing data are assumed to have progressed* HR=0.71; p=0.007 (44ug) HR=0.77; p=0.036 (22ug) Interferon beta-1a (22ug): 128/189 (67.7%) Interferon beta-1a (44ug): 118/184 (64.1%) Delayed treatment: 137/187 (73.3%) **Progression to EDSS score 6.0**** Interferon beta-1a (22ug): 42/189 (22.2%) Interferon beta-1a (44ug): 36/182 (19.8%) Delayed treatment: 32/186 (17.2%)	**Disability progression** (confimred at 3 months; 4 years' follow-up) *Participants with missing data are assumed to not have progressed* HR=0.80; p=0.119 (44ug) HR=0.89; p=0.379 (22ug) Interferon beta-1a (22ug): 108/189 (57.1%) Interferon beta-1a (44ug): 100/184 (54.3%) Delayed treatment: 104/187 (55.6%)	**Relative percentage change in T2 burden of disease (summed cross-sectional area of lesions in T2 scans)** (from baseline to LTFU) Interferon beta-1a (44ug): 5.0 (–64.7, 1055) Delayed treatment: 24.5 (–56.3, 869.2) p=0.002Ω ΩANCOVA adjusted for study site and T2 BOD at baseline. Includes baseline, 4 year data and LTFU data.	**Relative percentage change in T2 burden of disease (summed cross-sectional area of lesions in T2 scans)** (from baseline to LTFU) Interferon beta-1a (22ug): 17.4 (–52.5, 774.8) Delayed treatment: 24.5 (–56.3, 869.2) p=0.114Ω ΩANCOVA adjusted for study site and T2 BOD at baseline. Includes baseline, 4 year data and LTFU data.			**Mortality** Interferon beta-1a (22ug): 5/189 (2.7%) Interferon beta-1a (44ug): 1/184 (<1%) Delayed treatment: 2/187 (1%)
Rudick 2005/Rudic	**Disability progression** *Number of participants*	**Disability progression** *Number of participants*					**Discontinuation due to any reason** (during open-

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
k 2010/Herndon 2005	*reaching EDSS score 4.0* RR= 0.57, 95% CI, 0.43-0.75, p<0.0001 Early treatment: 35/79 (44.3%) Delayed treatment: 53/81 (65.4%)	*reaching EDSS score 6.0* RR= 0.69, 95% CI, 0.45-1.07, p=0.09 Early treatment: 23/79 (29%) Delayed treatment: 34/81 (42%) *Sustained progression∂ for 6 months* RR= 0.68, 95% CI, 0.41-1.14, p=0.14 Early treatment: 18/79 (22.8%) Delayed treatment: 27/81 (33.3%) ∂ Defined as a 1-point or greater worsening from baseline sustained for at least 6 months					label phase) Early treatment: 32/115 (27.8%) Delayed treatment: 34/103 (33%)
Ebers 2010 260 (69.9%)		**Disability progression** *Proportion reaching EDSS score 6*** Interferon beta-1b (250ug): 44/96 (45.8%) Interferon beta-1b (50ug): 33/85 (38.8%) Placebo: 36/79 (45.6%%) *Proportion reaching secondary progressive*			**Mortality** IFN 250ug vs. placebo: p=0.0049 IFN 50ug vs. placebo: p=0.0402 Interferon beta-1b (250ug): 6/111 (5.4%) Interferon beta-1b (50ug): 9/108 (8.3%) Placebo: 20/109 (18.4%)		**Fever** Interferon beta-1b (250ug): 58/96 (60.4%) Placebo: 31/79 (39.2%) **Injection-site reactions** Interferon beta-1b (250ug): 83/96 (86.5%) Placebo: 33/79 (41.8%) **Flu-like symptoms** Interferon beta-1b (250ug):

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		*MS*** Interferon beta-1b (250ug): 42/96 (43.8%) Interferon beta-1b (50ug): 28/85 (32.9%) Placebo: 34/79 (43%)					55/96 (57.3%) Placebo: 45/79 (57%) **Increased liver transaminases** Interferon beta-1b (250ug): 23/96 (24%) Placebo: 5/79 (6.3%)
Goodin 2012 366 (98.4%)					**Mortality** HR=0.532, 95% CI, 0.314-0.902; p=0.0173 (IFN 250ug vs. placebo) HR=0.540, 95% CI, 0.318-0.915; p=0.0202 (IFN 50ug vs. placebo) Interferon beta-1b (250ug): 22/122 (18%) Interferon beta-1b (50ug): 22/123 (17.9%) Placebo: 37/121 (30.6%)		
Johnson 2000		*Results only presented for early treatment group* **Annual relapse rate** ARR=0.42; 95% CI, 0.34-0.51					**Discontinuation due to any reason** (during open-label phase) Early treatment: 24/101 (23.8%) Delayed treatment: 32/107 (30%)
Freedmans 2005		**Disability progression** (proportion with 1 point EDSS increase)		**T2 active lesions** Interferon 44mcg vs delayed interferon			**Discontinuation due to adverse event during extension**

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		22mcg vs delayed 22mcg (p=0.94) 44mcg vs delayed 44mcg (p=0.17) Interferon 22mcg: 39 Interferon 44mcg: 35 Delayed interferon (22mcg): 46 Delayed interferon (44mcg): 40 **Mean relapse rate** 22mcg vs delayed 22mcg (p=0.96) 44mcg vs delayed 44mcg (p=0.32) Interferon 22mcg: 0.83 Interferon 44mcg: 0.77 Delayed interferon (22mcg): 0.84 Delayed interferon (44mcg): 0.86		44mcg (p=0.15) Interferon 22mcg vs delayed interferon 22mcg (p=0.69) Interferon 22mcg: 1.7 (3.3), median (mean) Interferon 44mcg: 1.3 (2.6), median (mean) Delayed interferon (22mcg): 1.7 (3.4), median (mean) Delayed interferon (44mcg): 2.0 (3.6), median (mean)			(N in each group unclear) Interferon 22mcg: 2 Interferon 44mcg: 4 Delayed interferon (22mcg): 0 Delayed interferon (44mcg): 1 Serious adverse events were balanced between groups. Those SAEs considered at least possibly related to medication included one patient on 22 mcg qw (vomiting) and five patients on 44 mcg qw (gastroenteritis, depression with suicide attempt, psychosis, MS exacerbation and Grave's disease). All SAEs were unique events except for three cases of depression on 22 mcg qw and two cases of cholelithiasis on 44 mcg qw.
Giovannoni 2014		**Annualised relapse rate** (during extension phase) Continuous treatment: 0.165; 95% CI, 0.105-0.259 Washout and re-initiation: 0.179; 95% CI, 0.123-0.261		**Number of gadolinium-enhancing T1 lesions** (during extension phase; 252 weeks' follow-up) Teriflunomide 14mg: 0.21 (0.62); mean, (SD) Delayed teriflunomide 14mg: 0.18 (0.55);			**Serious adverse events** Teriflunomide 14mg: 55/250 (22%) Delayed teriflunomide 14mg: 19/106 (17.9%) Teriflunomide 7mg: 62/254 (24.4%) Delayed teriflunomide 7mg: 30/130 (23.1%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		Delayed treatment: 0.302; 95% CI, 0.215-0.423 **<u>Proportion of patients who relapsed</u>** (during extension) Continuous treatment: 0.136; 95% CI, 0·087–0·209 Washout and re-initiation: 0.241, 95% CI, 0·175–0·327 Delayed treatment: 0.176, 95% CI, 0·125–0·245 **<u>Number with confirmed disability progression</u>** (during extension) Continuous treatment: 7/129 (5.4%) Washout and re-initiation: 10/132 (7.6%) Delayed treatment: 8/163 (4.9%)		mean, (SD) Teriflunomide 7mg: 0.56 (1.58); mean, (SD) Delayed teriflunomide 7mg: 0.6 (2.32); mean, (SD) **<u>T2 lesion volume (mL)</u>** (during extension phase; 252 weeks' follow-up) Teriflunomide 14mg: 14.67 (12.55); mean, (SD) Delayed teriflunomide 14mg: 17.36 (17.85); mean, (SD) Teriflunomide 7mg: 17.7 (19.35); mean, (SD) Delayed teriflunomide 7mg: 16.09 (14.74); mean, (SD)			**<u>Adverse events leading to death</u>** Teriflunomide 14mg: 1/250 (<1%) Delayed teriflunomide 14mg: 0/106 Teriflunomide 7mg: 1/254 (<1%) Delayed teriflunomide 7mg: 1/130 (<1%) **<u>Malignancies</u>** (neoplasms, glioma, cervical carcinoma, breast cancer, hepatic cancer, basal cell carcinoma, metastatic colon cancer) Teriflunomide 14mg: 4/250 (1.6%) Delayed teriflunomide 14mg: 1/106 (<1%) Teriflunomide 7mg: 3/254 (1.2%) Delayed teriflunomide 7mg: 2/130 (1.5%) **<u>Discontinuation due to adverse events</u>** Teriflunomide 14mg: 24/250 (9.6%) Delayed teriflunomide 14mg: 11/106 (10.4%) Teriflunomide 7mg: 29/254 (11.4%) Delayed teriflunomide 7mg:

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
							18/130 (13.8%)
Khatri 2011	**Estimated annualised relapse rate*** Continuous fingolimod (0.5mg): 0.18, 95% CI, 0.14-0.22 Continuous fingolimod (1.25mg): 0.20, 95% CI, 0.16-0.25 Delayed fingolimod: 0.33, 95% CI, 0.27-0.39 p<0.0001 for continuous treatment groups vs. delayed fingolimod group Continuous fingolimod (0.5mg) vs delayed fingolimod HR**=0·58; 95% CI, 0·45–0·74 Continuous fingolimod (1.25mg) vs delayed fingolimod HR=0·64; 95% CI, 0·50–0·82 *Months 0–24, estimated from a negative binomial regression model adjusted for treatment, country, number of			**Number of new or enlarged T2 lesions** Fingolimod (0.5mg): 0.9 (1.65), mean (SD) Delayed fingolimod (0.5mg): 0.7 (1.54), mean (SD) Fingolimod (1.25mg): 1.0 (2.3), mean (SD) Delayed fingolimod (1.25mg): 1.0 (1.87), mean (SD) **Number of gad-enhancing lesions on T1-weighted images** Fingolimod (0.5mg): 0.1 (0.44), mean (SD) Delayed fingolimod (0.5mg): 0.1 (0.34), mean (SD) Fingolimod (1.25mg): 0.2 (0.96), mean (SD) Delayed fingolimod (1.25mg): 0.2 (1.11), mean (SD) **Change in normalised brain volume** Fingolimod (0.5mg): -0.37 (0.67), mean (SD) Delayed fingolimod (0.5mg): -0.22 (0.64),	**Infectious adverse events** Fingolimod (0.5mg): 204/429 (47.6%) Delayed fingolimod (0.5mg): 91/167 (54%) Fingolimod (1.25mg): 199/420 (47.4%) Delayed fingolimod (1.25mg): 91/174 (52%) **Serious adverse event** Fingolimod (0.5mg): 19/429 (4.4%) Delayed fingolimod (0.5mg): 8/167 (5%) Fingolimod (1.25mg): 21/420 (5%) Delayed fingolimod (1.25mg): 21/174 (12%)	**Neoplasms** (benign, malignant, unspecified including cysts and polyps) Fingolimod (0.5mg): 6/429 (1.4%) Delayed fingolimod (0.5mg): 0/167 Fingolimod (1.25mg): 3/420 (0.7%) Delayed fingolimod (1.25mg): 1/174 (0.6%)	

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
	relapses in the 2 years before enrolment, and core baseline EDSS score. **Calculated from a Cox proportional hazard model adjusted by treatment, country, number of relapse in the previous 2 years before enrolment and core baseline EDSS			mean (SD) Fingolimod (1.25mg): -0.35 (0.67), mean (SD) Delayed fingolimod (1.25mg): -0.14 (0.60), mean (SD)			
Cohen 2015	**Risk of relapse** Continuous fingolimod (0.5mg) vs delayed fingolimod HR=0·65; p<0.001	**Estimated annualised relapse rate*** Continuous fingolimod (0.5mg): 0.16, 95% CI, 0.12-0.19 Delayed fingolimod: 0.20, 95% CI, 0.16-0.25 p=0.101 for continuous treatment vs. delayed treatment **Disability progression (confirmed at 3 months)**** HR=0.94, 95% CI, 0.71-1.26); p=0.687 Continuous fingolimod (0.5mg): 94 (22%) Delayed fingolimod: 91 (21%) **Disability progression (confirmed at 6**		**Number of new/newly enlarging T2 lesions** Continuous fingolimod (0.5mg): 0.9 (2.7), mean (SD) Delayed fingolimod: 1.0 (4.4), mean (SD) **Number of GAD T1 lesions** Continuous fingolimod (0.5mg): 0.3 (1.1), mean (SD) Delayed fingolimod: 0.4 (2.7), mean (SD) **Mean percent change in brain volume** Continuous fingolimod (0.5mg): -1.01 Delayed fingolimod: -0.96 p=0.937		**Malignancies (basal cell carcinoma, breast cancer)** Fingolimod (0.5mg): 8/356 (2.24%) Delayed fingolimod (0.5mg): 1/167 (0.6%)	**Discontinuation of study drug due to any reason** Fingolimod (0.5mg): 75/356 (21.1%) Delayed fingolimod (0.5mg): 44/167 (26.3%) Fingolimod (1.25mg): 85/330 (25.8%) Delayed fingolimod (1.25mg): 51/174 (29.3%) **Discontinuation of study drug due to adverse event** (including abnormal laboratory values) Fingolimod (0.5mg): 35/356 (9.8%) Delayed fingolimod (0.5mg): 11/167 (6.6%) Fingolimod (1.25mg): 35/330 (10.6%) Delayed fingolimod (1.25mg): 32/174 (18.4%)

Study ID N (% of original cohort)†	Relapse and disability progression		MRI		Safety		
		<u>months)</u> HR=1.08, 95% CI, 0.77-1.51); p=0.674 Continuous fingolimod (0.5mg): 73 (17%) Delayed fingolimod: 63 (15%) *From start of extension to end of study. P-value from negative binomial regression model, adjusted for treatment, pooled country, number of relapses in the previous 2 yeas before enrollment and original trial baseline EDSS **From original trial baseline to end of extension study. HRs and p values from the Cox proportional hazards model adjusted for treatment, pooled country, core baseline EDSS and age					**<u>Serious adverse events</u>** Fingolimod (0.5mg): 55/356 (15.4%) Delayed fingolimod (0.5mg): 21/167 (12.6%)

HR= Hazard ratio
RR= relative risk
CI= confidence intervals
DMF= BID and TID dimethyl dumarate groups confirmed
†Proportion of original cohort who completed the extension phase
**No statistical anaysis reported/carried out
¥Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40).

[β]Based on negative binomial regression, adjusted for baseline number of new or newly enlarging T2 lesions
[δ]Percent reduction based on group mean and p-value based on multiple logit regression, adjusted for baseline number of Gd+ lesions
¤Annualized relapse rate (ARR) estimated from a negative binomial model adjusted for treatment, pooled country, number of relapses in the 2 years before enrollment, and FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) baseline Expanded Disability Status Scale score; p values are for the ARR ratio between active treatment ARR and placebo ARR.
ΔTime to 3-month confirmed disability progression based on EDSS score with Kaplan-Meier estimate of patients free from progression at EoS
‡Cumulative number of new or newly enlarged T2 lesions compared using a negative binomial model adjusted for treatment, FREEDOMS baseline volume of T2 lesions, and pooled country
[Æ]Cumulative number of gadolinium (Gd)-enhancing T1 lesions from month 0 to EoS, including patients with all assessments during that time interval; p values are for comparisons with the placebo–fingolimod group
δBetween-group comparisons of changes in brain volume from month 0 to end of study in the FTY720 Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) intent-to-treat (ITT) population. Percentage brain volume change was compared using a rank analysis of covariance adjusted by treatment, normalized brain volume at FREEDOMS baseline, and country

Table 3: Results of extension studies comparing early and delayed treatment with interferon in PPMS

Study ID N (% of original cohort)†	Relapse and disability progression	MRI	Safety
Tur 2011	**Disability progression*** (from original trial baseline to end of extension) Early treatment: 70.97% Delayed treatment: 67.74% Signed rank test indicated not significant between group difference (p=0.78) **Cognitive performance** (from original trial baseline to end of extension) *PASAT* Wilcoxon rank sum test indicated no difference between groups on the PASAT for changes from baseline to 5 year follow-up (p=0.24) *at least 1–EDSS point increase if the baseline EDSS score was 5 or lower or 0.5-point increase if the baseline EDSS score was 5.5 or higher (1 step change)	**Change in T2 lesion volume** (from original trial baseline to end of extension) Early treatment: 2265.9 (−303.30 to 12 754.40); median change (range) Delayed treatment: 2986.90 (−9773.30 to 13 226.50); median change (range) Signed rank test indicated no significant differnce between treatment groups (p=0.78) **Change in brain parenchymal fraction** (from original trial baseline to end of extension) Early treatment: -1.78 (−6.99 to 1.29); median change (range) Delayed treatment: −3.16 (−6.87 to 2.37); median change (range) Signed rank test indicated significantly lower brain atrophy in the early treatment group (p=0.004)	Not reported

Study ID N (% of original cohort)†	Relapse and disability progression	MRI	Safety

Question 4. Monitoring treatment response

Table 1: Positive and negative predictive value of three best performing criteria identified in the review by Rio 2016

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Rio 2016	New T2 ≥1	EDSS worsening	4 to 4.8 years	K=2	48%	93.8%
Rio 2016	New T2 ≥2	EDSS worsening	4 to 4.8 years	K=2	55%	87.3%
Rio 2016	ModRio score ≥2	EDSS worsening	4 years	K=2	50%	75.5%

Table 2: Positive and negative predictive value of criteria located in primary studies from the updated search

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Hyun 2015	Rio Score ≥2	EDSS worsening	3 years	K=1	92%	93%
Hyun 2015	ModRio score ≥2	EDSS worsening	3 years	K=1	86%	93%
Sormani 2016	MAGNIMS ≥1	Treatment failure	3 years	K=1	34%	83%
Sormani 2016	MAGNIMS ≥1	EDSS worsening	3 years	K=1	26%	86%

Table 3: Positive and negative predictive value of NEDA from Rottstein 2015

Study ID	Criteria	Outcome	Follow-up	Studies	Positive predictive value	Negative predictive value
Rottstein 2015	NEDA	Absence of disability worsening	7 years	K=1	71.7%	40.7%-43.1%

Question 10. Treatment in special situations: pregnancy

Table 4. Impact of exposure to DMTs on pregnancy outcomes

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations¥	Neonatal death	
Amato 2010	IFNb	*Exposed*	OR=1.14, 95% CI 0.41 to 3.15, p=0.803)	8% (7/88)	NR	NR	Up to 2 years
		Unexposed		6.3% (20/318)			
Boscovic 2005	IFNb	*Exposed*	NR	39% (9/23)	9% (2/23)	4% (1/23)	Not reported
		Unexposed		19% (4/21)	5% (1/21)	0%	
Coyle 2014	IFNb	*Exposed*	5.1% (3/59)[a]	11.5% (11/96)	5.8% (5/96)	NR	17 weeks post-partum
Romero 2015	IFNb	*Exposed*	0.2% (1/423)[b]	14.4% (61/423)	1.9% (8/423)	NR	Not reported
Thiel 2016	IFNb	*Exposed*	OR 0.77 (0.26-2.22 95%CI)[b]	9.6% (24/251)	3.1% (7/251)	NR	52 weeks postpartum
		Unexposed		6.7% (13/194)	5.5% (10/194)		
Herbstritt 2016	GA	*Exposed*	NR	8.6% (13/151)	2.2% (3/151)	NR	26 weeks postpartum
		Unexposed		6.3% (6/95)	6.7% (6/95)		
Giannini 2012	IFNb and GA	*Exposed (IFN)*	NR	8% (7/87)	NR	NR	Not reported
		Exposed (GA)		6% (1/17)			
		Unexposed		6% (20/311)			

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations¥	Neonatal death	
Weber-Schoendorfer & Schaefer 2009	IFNb and GA	*Exposed (GA)*	NR	4% (1/26)	8% (2/26)	NR	8 weeks post-partum
		Exposed (IFN)		12% (7/60)	6% (2/54)		
		Unexposed		10% (6/61)	9% (5/57)		
Ebrahimi 2015	NTZ IFNb and GA	*Exposed (NTZ)*	7.8% (6/77)	17.3% (17/98)	3.9% (3/77)	NR	6 months post-partum
		Exposed (IFN or GA)	7.4% (5/68)	21.1% (20/95)	1.4% (1/69)		
Hellwig 2011	NTZ	*Exposed*	NR	14.3% (5/35)	2.9% (1/35)	NR	6 months post-partum
		Unexposed		4.3% (1/23)	4.3% (1/23)		
Hellwig 2012	IFNb and GA	*Exposed (IFN)*	NR	NR	3.8% (3/78)	NR	NR
		Exposed (IGA)			4.9% (2/41)		
		Unexposed			3.2% (7/216)		
De La Heras 2007	iDMTs	*Exposed*	NR	17.6% (6/34)	No abnormalities or obstetric complications were recorded	NR	At least 3 months
		Unexposed		20.4% (11/54)			
Fernandez Liguori 2009	IFNb and GA	*Exposed*	5.8%[b]	15.6% (22/141)	4.8% (1.6-10.9%)	NR	NR
Lu 2012	IFNb and	*Exposed*	NR	NR	0% (0/21)	NR	NR

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations$^{\Psi}$	Neonatal death	
	GA	*Previously treated*			8.8% (7/80)		
		DMD naive			5.4% (17/317)		
Fragoso 2013	IFNb and GA	*Exposed (IFN)*	0% (0/17)	0% (0/17)	0% (0/17)	0% (0/17)	46.5 months
		Exposed (GA)	4.9% (2/41)	4.9% (2/41)	2.4% (1/41)	2.4% (1/41)	
		Unexposed	2.2% (2/89)	2.2% (2/89)	0% (0/89)	0% (0/89)	
Gold 2015	DMF	*Exposed (DMF)*	NR	7.7% (3/39)	NR	NR	NR
		Placebo		15.4% (2/12)			
Karlsson 2014	FTY	Exposed$^{\Delta}$	NR	24% (12%–41%), (9/37)	5% (0.7%-18%), (2/37)§	NR	NR
Kieseier & Benamor 2014	Teriflunomide	Exposed	NR	18.8% (13/39)	No malformations noted out of 27 live births	NR	NR
Patti 2008	IFNb	*Exposed*	No significant difference between groups in birth weight	0% (0/14)	NR	NR	Until 18 months post-partum
		Previously treated		0% (0/7)			
		DMD naive		5.9% (1/17)			

¥Drug received by pregnant women in the exposed group.
†Outcomes are presented as reported in the published article; no additional analyses carried out. ‡Length of follow-up after pregnancy
ΨDefinitions: *Boscovic 2005* – major malformations (not defined); *Coyle 2014* – congenital malformations; *Romero 2015* – major and minor birth defects; *Thiel 2016 & Herbstritt 2016* - specified as a defect in organogenesis, major malformations as structural defects of the body and/or organs that impair viability and/or require intervention. Minor malformation was defined as small structural developmental disturbances that do not impair viability and do not need to be treated; *Weber-Schoendorfer & Schaefer 2009* – any birth defect: defined as structural abnormalities of medical, surgical, or cosmetic relevance - classified according to Merks et al. and Rasmussen, et al. Genetic syndromes were excluded; *Hellwig 2011* - NTZ: one boy with hexadactyly was born (minor malformation), Control: One girl suffered from trisomia 21 with ventricular septum defect; *Fragoso 2013* – bone malformation (not defined); *Karlsson 2014* - unilateral bowing of tibia and acrania
◊ Low birth weight was defined as <2,500g, unless specified according to the following: **(a)** Infant size was classified as 'small', 'appropriate' or 'large' for gestational age

Study ID	Drug¥	Groups	Outcomes†				Follow-up
			Low birth weight◊	Spontaneous abortion	Malformations₹	Neonatal death	
based on HCP assessment, **(b)** small for gestational age **Δ** No valid comparator. Out of 11 participants who had received placebo during the clinical trial, 9 were elective abortions leaving 2 pregnancies as the control group. **§** Out of 24 elective abortions, n=4 were due to complications: tetralogy of Fallot (n=1); ectopic/tubal pregnancy (n=1); intrauterine death (n=1); pregnancy not developing per standard n=1							

Appendix 10_Results of the consensus process

START ROUND 1 (e-mail): A total of 18 statements were circulated:
- 2 statements were accepted without further modification
- 16 were modified based on comments made by the experts
- 2 new statement was proposed

END ROUND 1:
- 2 statements were incorporated in the GL document
- 18 statements were considered for consensus in round 2

START ROUND 2 (face to face meeting): A total of 18 statements (16 modified + 2 new) were considered for consensus:
- 9 were accepted without further modification
- 6 were accepted after small modifications
- 3 were postponed to a 3rd round of consensus because of time limitations

END ROUND 2:
- 15 statements were incorporated in the GL document
- 3 statements were considered for round 3

START ROUND 3 (e-mail): Three statements were circulated:
- 2 statements were accepted without further modification
- 1 statement was accepted after small modifications

END ROUND 3:
- 3 statements were incorporated in the GL document

	Final agreement*			
Statement	Low (1-3)	Medium (4-6)	High (7-9)	
R1. The entire spectrum of DMDs should be prescribed only in centres with adequate infrastructure to provide: - Proper monitoring of patients - Comprehensive assessment - Detection of side effects and ability to promptly address them.			100%	Consensus statement
R2. Offer interferon or glatiramer acetate to patients with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil MS criteria.		18.2%	81.8%	Strong recommendation
R3. Offer early treatment with DMDs in patients with active relapsing-remitting MS as defined by clinical relapses and/or MRI activity (active lesions -contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). Also includes CIS fulfilling current diagnostic criteria of MS.		5.9%	94.1%	Strong recommendation
R4. For active relapsing-remitting MS, choosing between the wide range of available drugs (interferon beta-1b, interferon beta-1a -sc, im-, peginterferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, daclizumab, natalizumab, alemtuzumab and ocrelizumab), from the modestly effective to the highly efficacious, will depend on the following factors, in discussion with the patient: - Patient characteristics and comorbidities - Disease severity/activity - Drug safety profile - Accessibility of the drug		5.9%	94.1%	Consensus statement
R5. Consider treatment with interferon-1a (sc) or -1b in patients with active SPMS taking into account, in discussion with the patient, the efficacy, safety, and tolerability profile of these drugs.		18.2%	81.8%	Weak recommendation
R6. Consider treatment with mitoxantrone in patients with active secondary progressive MS taking into account, in discussion with the patient, the efficacy, and specifically the safety and tolerability profile of this agent.		18.2%	81.8%	Weak recommendation
R7. Consider treatment with ocrelizumab or cladribine for patients with			100%	Weak recommendation

active secondary-progressive MS.				
R8. Consider treatment with ocrelizumab for patients with primary-progressive MS.			100%	Weak recommendation
R9. Consult the Summary of Product Characteristics (SPC) for dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harms.			100%	Consensus statement
R10. Consider combining MRI with clinical measures when evaluating disease evolution in treated patients.			100%	Consensus statement
R11. When monitoring treatment response in patients treated with DMDs, perform a standardized reference brain MRI usually within six months of treatment onset and compare it with a further brain MRI performed typically 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the following aspects: - the drug's mechanism of action (particularly the speed of action) - disease activity (including clinical and MRI measures)		17.6%	82.4%	Consensus statement
R12. When monitoring treatment response in patients treated with DMDs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method supplemented by gadolinium enhancing lesions for monitoring treatment response. Evaluation of these parameters requires: - high-quality, standardized MRI scans - interpretation by highly qualified readers with experience in MS			100%	Consensus statement
R13. When monitoring treatment safety in patients treated with DMDs, perform a standardized reference brain MRI: - every year in low risk PML patients - more frequent MRIs (on a 3 to 6 monthly basis) in high risk PML patients (JCV positive, natalizumab treatment duration over 18 months) - in patients with high risk of PML who switch drugs, at the time that the current treatment is discontinued and after the new treatment is started.			100%	Consensus statement
R14. Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity assessed as recommended in questions 4-5 of this guideline.			100%	Strong recommendation

R15. When deciding on which drug to switch to, in consultation with the patient, consider the following factors: - Patient characteristics and comorbidities - Drug safety profile - Disease severity/activity			100%	Consensus statement
R16. When treatment with a highly efficacious drug is stopped, either due to inefficacy or safety concerns, consider starting another highly efficacious drug. When starting the new drug, take into account the following factors: - Disease activity (clinical and MRI), the greater the activity, the higher the urgency to start new treatment. - Half life and biological activity of the previous drug. - The potential for resumed disease activity or even rebound (particularly with natalizumab).			100%	Weak recommendation
R17. In treatment decisions, clinicians should consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab.			100%	Strong recommendation
R18. Consider continuing a DMD if a patient is stable (clinically and on MRI) and shows no safety or tolerability issues.		10%	90%	Weak recommendation
R19. Advise all women of childbearing potential that DMDs are not licensed for pregnancy, except glatiramer acetate 20 mg/ml.			100%	Consensus statement
R20. For women planning a pregnancy, if there is a high risk of disease reactivation, consider using interferon or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered.			100%	Weak recommendation
R21. For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who, despite this advice, still decide to become pregnant or have an unplanned pregnancy: -Treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications. -Treatment with alemtuzumab could be an alternative therapeutic option for		12%	88%	Weak recommendation

planned pregnancy in very active cases, provided that a 4-month interval is strictly observed from the latest infusion until conception.				

*Based on the result of the Likert scale grouped into 3 categories (1–3: inappropriate strategy; 4–6: uncertain; 7–9: appropriate strategy). Agreement cut-off point 80%