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