Appendix 5_GRADE tables

Review question 1

1. Interferon compared with placebo for clinically isolated syndrome

			Quality asse	ssment			No of pa	ntients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Time to co	nversion to CI	OMS (104 weeks	s' follow-up) (follow	-up mean 104 wee	ks)							
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	HR 0.49 (0.38 to 0.64)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Conversio	n to CDMS (fol	low-up 104-156	weeks)									
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/363 (41.9%)	(60.3%)	RR 0.71 (0.61 to 0.82)	175 fewer per 1000 (from 109 fewer to 235 fewer) 179 fewer per 1000 (from 111	⊕⊕⊕O MODERATE	CRITICAL
								61.6%		fewer to 240 fewer)		
New GAD I	lesions (numb	er of patients fr	ee) (follow-up mear	n 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 lesion	ns (mean num	ber) (78 weeks'	follow-up) (follow-ι	ıp 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 les	ions (number	of patients free) (follow-up mean 1	04 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 enlargir	g lesions (mea	n number) (78 week	s' follow-up) (follo	ow-up mean 78 w	eeks; Better indica	ted by lowe	r 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 volu	me (follow-up r	mean 104 weeks; Be	etter 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	e number of ne	ewly active lesion	ons (mean number)	(follow-up mean	104 weeks; Better	indicated by lowe	r 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 wee	ks; Better indicate	d 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
Discontinu	ation due to a	ny reason (follo	w-up 104-156 week	rs)								

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)		
Discontin	uation due to s	ide effects (foll	ow-up 104-156 wee	ks)								
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)		
Discontin	uation of study	drug due to sid	de effects (follow-u	p 104-156 weeks)								
2	randomised trials	no serious risk of bias	very serious⁵	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)		
Discontin	uation of study	drug due to an	y reason (follow-u	p 104-156 weeks)	•	•	<u>.</u>	•	•			
2	randomised trials		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-eve	ent) (follow-up 1	04-156 weeks)									
2	randomised trials		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 (l	PASAT-3") (follo	ow-up mean 104 w	eeks; Better indica	ated by lower valu	ues)						
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	none	273	166	-	MD 1.4 higher (0.29 to 2.51 higher)	⊕⊕⊕O MODERATE	IMPORTANT

2. Glatiramer acetate compared with placebo for clinically isolated syndrome

			Quality asse	essment			No of pation	ents		Effect	- Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glatiramer acetate	Placebo	Relative (95% CI)	Absolute	Quanty	importunee		
Time to co	onversion to C	DMS (follow-u	ip median 156 wee	eks)					·					
1	randomised serious no serious no serious no serious no moserious no mo													
Discontin	uation due to a	any reason (fol	low-up median 150	6 weeks)										

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

1		no serious risk of bias		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)	O O O O	IMPORTANT
								9.7%		64 more per 1000 (from 2 more to 164 more)		
Discontin	uation due to	side effects (fol	low-up median 15	6 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 asses	ssment			No of pati	ients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriflunomide	Placebo	Relative (95% CI)	Absolute	quanty	mportanee
Time to cor	version to CDI	MS (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 (num	nber of part	ticipants) (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 p	rogression (nu	mber of pa	rticipants)									
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 (m	ean change fro	m baseline	e) (follow-up mean 10	8 weeks; Better inc	dicated by lo	wer 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 lesion	s (mean numbe	er of lesion	s per MRI scan) (foll	ow-up mean 108 we	eeks; Better i	indicated by lower v	/alues)					
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 co	omponent (volu	ıme) (mear	change from baseli	ne) (follow-up mea	n 108 weeks;	Better indicated by	lower values)				<u> </u>	
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
Discontinua	ation of study o	rug due to	any reason (follow-	ip mean 108 weeks	5)		•	!				
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)		
Discontinua	ation of study o	lrug due to	side effects (follow-	up mean 108 weeks	s)							
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 (n	umber of partic	cipants) (fo	llow-up mean 108 we	eeks)								
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)	$\oplus \oplus OO$	IMPORTANT

								39.4%		43 more per 1000 (from 43 fewer to 158 more)	LOW	
Serious infe	ection (number	of particip	ants) (follow-up mea	n 108 weeks)								
	randomised trials	serious ¹		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 (fo	llow-up mean	108 weeks										
	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)		

Review question 2

1. Interferon compared with placebo

			Quality asse	essment			No of pa	ntients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Relapse fi	ree (number of	participants) (follow-up 48 weeks)								
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none		358/500 (71.6%)	RR 1.15 (1.08 to 1.23)	107 more per 1000 (from 57 more to 165 more)	O O O O	CRITICAL
								71.6%		107 more per 1000 (from 57 more to 165 more)		
Relapse fi	ree (number of	participants) (follow-up 104 week	rs)								
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 fi	ree (number of	participants) -	156 weeks FU (foll	ow-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)		
Annualise	ed relapse rate	(follow-up 48-1	04 weeks; Better in	dicated 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

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.

	trials		inconsistency	indirectness	imprecision					lower)	MODERATE	
Disability	progression co	onfirmed at 3 m	onths (number of	participants wors	ened) (follow-up	18 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 co	onfirmed at 6 m	onths (number of	participants wors	ened) (follow-up	104 weeks)		l.				
2	randomised	serious ⁶	no serious	no serious	serious ³	none	53/532	75/537	RR 0.71 (0.51	41 fewer per 1000 (from 3		CRITICAL
	trials		inconsistency	indirectness			(10%)	(14%)	to 0.98)	fewer to 68 fewer)	LOW	
								21.8%		63 fewer per 1000 (from 4 fewer to 107 fewer)		
Disability	progression (r	umber of parti	cipants worsened)	(follow-up 156 we								
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)		
Discontin	uation due to s	ide effects - 48	weeks FU (follow-	ıp 48 weeks)	•	•						
1	randomised	no serious risk	no serious	no serious	serious ³	none	24/512	5/500	RR 4.69 (1.8 to	37 more per 1000 (from 8		CRITICAL
	trials	of bias	inconsistency	indirectness			(4.7%)	(1%)	12.19)		MODERATE	
								1%		37 more per 1000 (from 8 more to 112 more)		
Discontin	uation due to a	ny reason (follo	ow-up 48 weeks)	•								
1	randomised		no serious	no serious	serious ³	none	74/512	44/500	RR 1.64 (1.15	56 more per 1000 (from 13		CRITICAL
	trials	of bias	inconsistency	indirectness			(14.5%)	(8.8%)	to 2.34)	<u> </u>	MODERATE	
								8.8%		56 more per 1000 (from 13 more to 118 more)		
Discontin	uation due to s	ide effects (follo	ow-up 104 weeks)									
3	randomised trials	serious ²	no serious	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
	uriais		inconsistency	indirectness			(3.3%)		10 2.80)	12 more per 1000 (from 1	LOW	
								1.7%		more to 32 more)		
Discontin			ow-up 104 weeks)	1				T			ı	
2		no serious risk		no serious	serious ³	none	110/820	109/638	RR 0.84 (0.65	27 fewer per 1000 (from 60	MODERATE	CRITICAL
	trials	of bias	inconsistency	indirectness			(13.4%)	(17.1%)	to 1.07)	fewer to 12 more) 15 fewer per 1000 (from 34	MODERATE	
								9.6%		fewer to 7 more)		
Discontin	uation due to s	ide effects (follo	ow-up 156 weeks)									
1	randomised	serious ⁴	no serious	no serious	serious ³	none	10/124	2/123	RR 4.96 (1.11	64 more per 1000 (from 2		CRITICAL
	trials		inconsistency	indirectness			(8.1%)	(1.6%)	to 22.17)	more to 344 more)	LOW	

trials inconsistency indirectness (18.5%) (19.5%) to 1.59) fewer for 115 more) Lesion volume (mm3) (follow-up 156 weeks; Better indicated by lower values) I randomised prious-57 in on serious indirectness indire			1		1		1	1	1	T		ı	ı
Discontinuation due to any reason (follow-up 156 weeks) In cardomised Serious In oscious Inconsistency Indirectness Indirectness Inconsistency Indirectness Indirectne									1.6%				
Traidomised Serious Do Se									1.070		more to 339 more)		
trials inconsistency inclinectness (18.5%) (19.5%) to 1.59) fewer to 115 more) 10 fewer per 1000 (from 84 fewer to 115 more) 10 fewer to 10 fewer per 1000 (from 84 fewer to 115 more) 10 fewer to 10 fewer	Discontinu	iation due to a	ny reason (foll	ow-up 156 weeks)									
Lesion volume (mm3) (follow-up 156 weeks; Better indicated by lower values) In andomised trials Tandomised erious In oserious In oserious Indicated by lower values Indicated by lower v	1	randomised	serious ⁴	no serious	no serious	serious ³	none	23/124	24/123	RR 0.95 (0.57	10 fewer per 1000 (from 84		CRITICAL
Lesion volume (mm3) (follow-up 156 weeks; Better indicated by lower values) I randomised I		trials		inconsistency	indirectness			(18.5%)	(19.5%)	to 1.59)	fewer to 115 more)	LOW	
Lesion volume (mm3) (follow-up 156 weeks; Better indicated by lower values) Indicated by lower values Indica									10.50/		10 fewer per 1000 (from 84		
Tandomised Serious									19.5%		fewer to 115 more)		
trials	Lesion vol	ume (mm3) (f	ollow-up 156 w	eeks; Better indic	ated by lower valu	ies)							
trials monsistency indirectness molecular by lower values monsistency indirectness molecular by lower values molecular by lowe				,			none	134	123	_	MD 26.5 lower (90.6 lower		CRITICAL
Lesion volume (mm3) (follow-up 104 weeks; Better indicated by lower values)													
Tandomised trials	Lesion vol	ume (mm3) (f	ollow-up 104 w	<u> </u>	ated by lower valu	ies)				L	9 /	L	L
Inconsistency Indirectness Inconsistency Indirectness In		. , ,					none	82	82	_	MD 48 3 lower (169 42		CRITICAL
New or newly enlarging T2 lesions (mean number) (follow-up 48 weeks; Better indicated by lower values) randomised ran			scrious			scrious	none	62	02	_			CRITICILE
Tandomised Serious no serious indirectness serious Nober			T2 logiona (ma	<u> </u>		tton indicated by	lower volves)				iower to 72.02 ingher)	EO II	
trials inconsistency indirectness imprecision lower) MODERATE T2 active lesions (number of participants with no activity) (follow-up 104 weeks) randomised rials r								157	176	I	MD 7.21 (0.05 + 5.75		CDITICAL
To active lesions (number of participants with no activity) (follow-up 104 weeks) I randomised trials serious serious inconsistency indirectness in			serious.				none	457	4/6	-	-		
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trials inconsistency indirectness (24.8%) (8.7%) 4.63) more to 316 more) LOW	12 active I			-				T	ı	T		T	T
Combined unique active lesions (number of participants with no activity) (follow-up 104 weeks) 2 randomised trials serious no serious inconsistency indirectness imprecision randomised trials serious no serious inconsistency indirectness imprecision roserious ro	1		serious ⁸			serious ³	none			,			CRITICAL
Combined unique active lesions (number of participants with no activity) (follow-up 104 weeks) 2		trials		inconsistency	indirectness			(24.8%)	(8.7%)	4.63)	,	LOW	
Combined unique active lesions (number of participants with no activity) (follow-up 104 weeks) 2									8 7%		157 more per 1000 (from 60		
randomised trials serious serious serious inconsistency indirectness serious serious indirectness serious serious indirectness serious serious indirectness serious serious indirectness indirectness serious indirectness indirec									0.770		more to 316 more)		
trials inconsistency indirectness (36.4%) (12.1%) to 5.92) more to 596 more (1.0W) 12.1% 12.1% 10.592) more to 596 more LOW	Combined	unique active	e lesions (numb	er of participants	with no activity) (follow-up 104 we	eks)						
Percent brain volume change (follow-up 48 weeks; Better indicated by lower values) 1	2	randomised	serious ⁸	no serious	no serious	serious ³	none	48/132	8/66	RR 2.97 (1.49	239 more per 1000 (from 59		CRITICAL
Percent brain volume change (follow-up 48 weeks; Better indicated by lower values) I randomised trials no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious indirectness imprecision no		trials		inconsistency	indirectness			(36.4%)	(12.1%)	to 5.92)		LOW	
Percent brain volume change (follow-up 48 weeks; Better indicated by lower values) I randomised trials no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious inconsistency indirectness imprecision no serious indirectness imprecision no									10.10/	1	238 more per 1000 (from 59		
I randomised trials no serious no serious no serious no noe no									12.1%				
I randomised serious no serious inconsistency indirectness imprecision none 512 500 - MD 0.1 lower (0.2 lower to 0 higher) MODERATE Percent brain volume change (follow-up 104 weeks; Better indicated by lower values) I randomised serious no serious inconsistency indirectness imprecision none 447 450 - MD 0.11 lower (0.28 lower to 0.06 higher) MODERATE Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) I randomised serious no serious inconsistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICA trials inconsistency indirectness imprecision lower) Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)	Percent br	ain volume ch	nange (follow-u	p 48 weeks: Bette	r indicated by low	er values)		<u> </u>	<u>.</u>				·
trials inconsistency indirectness imprecision higher) MODERATE Percent brain volume change (follow-up 104 weeks; Better indicated by lower values) I randomised serious no serious no serious inconsistency indirectness imprecision none 447 450 - MD 0.11 lower (0.28 lower to 0.06 higher) MODERATE Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) I randomised serious no serious no serious no serious inconsistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICA inconsistency indirectness imprecision lower) Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)			1 .	<u> </u>		· ·	none	512	500	_	MD 0.1 lower (0.2 lower to 0.		CRITICAL
Percent brain volume change (follow-up 104 weeks; Better indicated by lower values) I randomised serious no serious no serious inconsistency indirectness imprecision Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) I randomised serious no seriou			serious				none	312	300				
1 randomised serious no serious no serious no serious inconsistency indirectness imprecision none 447 450 - MD 0.11 lower (0.28 lower to 0.06 higher) MODERATE Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) 1 randomised serious no serious no serious no serious none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICA inconsistency indirectness imprecision none 147 450 - MD 1.44 lower (1.97 to 0.91 CRITICA inconsistency indirectness imprecision none 147 450 - MODERATE Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)			ange (follow-11										
trials inconsistency indirectness imprecision to 0.06 higher) MODERATE Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) 1 randomised serious no serious no serious no serious inconsistency indirectness imprecision Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)				-		-	none	117	450		MD 0.11 lower (0.28 lower		CDITICAL
Cumulative number of GdE lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values) 1			serious				none	447	430	-			
1 randomised serious no serious no serious no serious none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL minimum consistency indirectness imprecision none 447 450 - MD 1.44 lower (1.97 to 0.91 CRITICAL			CdE lasiana ada	ļ			.4	-)			to 0.00 higher)	MODERATE	
trials inconsistency indirectness imprecision lower) MODERATE Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)							-		150	l	107 000		an imia : z
Cumulative number of new/enlarged T2 lesions at months 12 and 24 (follow-up 104 weeks; Better indicated by lower values)			serious ⁵				none	447	450	-	*		
			L	<u> </u>					<u> </u>		lower)	MODERATE	
11 randomised serious no serious no serious no serious none MA7 A50 MD 6.66 lower (9.04 to 4.29					ns 12 and 24 (follow		Better indicated by	lower value	1	,			
		randomised	serious ⁹	no serious	no serious	no serious	none	447	450	-	MD 6.66 lower (9.04 to 4.28		CRITICAL
trials inconsistency indirectness imprecision lower MODERATE				inconsistency	indirectness	imprecision					lower)	MODERATE	

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.

2. Glatiramer acetate compared with placebo

			Quality ass	essment			No of pati	ents		Effect	Ovolity	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glatiramer acetate	Placebo	Relative (95% CI)	Absolute	Quality	importance
Relapse fi	ree (number o	f participants)	(follow-up 52-104	weeks)								
3	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	1006/1418 (70.9%)	550/950 (57.9%) 59%	RR 1.17 (1.1 to 1.24)	98 more per 1000 (from 58 more to 139 more) 100 more per 1000 (from 59 more to 142 more)	□□□□ MODERATE	CRITICAL
Annualise	d relance rate	(follow-up 52-	 96 weeks; Better i	ndicated by lower	r values)					more to 142 more)		
2	randomised trials	· -	no serious inconsistency	no serious indirectness	no serious imprecision	none	1293	824	-	MD 0.14 lower (0.21 to 0.06 lower)	OODERATE	CRITICAL
Disability	progression (number of part	ticipants worsened	l) (follow-up 96-1	04 weeks)							
2	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	82/475 (17.3%)	98/489 (20%) 22.8%	RR 0.86 (0.66 to 1.11)	28 fewer per 1000 (from 68 fewer to 22 more) 32 fewer per 1000 (from 78 fewer to 25 more)	LOW	CRITICAL
Discontin	uation due to a	 anv reason (fol	low-up 52 weeks)							lewer to 23 more)		
1	randomised trials	no serious risk	_	no serious indirectness	serious ³	none	84/943 (8.9%)	31/461 (6.7%) 6.7%	RR 1.32 (0.89 to 1.97)	22 more per 1000 (from 7 fewer to 65 more) 21 more per 1000 (from 7 fewer to 65 more)	OODERATE	CRITICAL
Discontin	uation due to	any reason (fol	low-up 06-104 wed	eks)				<u>-</u>				
2	randomised trials					none	87/485 (17.9%)	102/489 (20.9%) 18.5%	RR 0.86 (0.66 to 1.11)	29 fewer per 1000 (from 71 fewer to 23 more) 26 fewer per 1000 (from 63 fewer to 20 more)		CRITICAL
Discontin	uation due to	side effects (fol	low-up 52 weeks)	<u> </u>		<u> </u>		-				1
1	randomised trials	no serious risk		no serious indirectness	serious ³	none	10/360 (2.8%)	11/363 (3%)	RR 0.92 (0.39 to 2.13)		O O O O	CRITICAL

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

	1	ı	1	1	1	1			1			
								3%		2 fewer per 1000 (from 18		
										fewer to 34 more)		
Discontinu	uation due to	· · · · · · · · · · · · · · · · · · ·	llow-up 96-104 wee	eks)						<u>, </u>		
2	randomised	serious1	no serious	no serious	serious ³	none	34/1068	7/587	RR 2.63 (1.17	19 more per 1000 (from 2		CRITICAL
	trials		inconsistency	indirectness			(3.2%)	(1.2%)	to 5.9)	more to 58 more)	LOW	
								1.1%		18 more per 1000 (from 2		
								1.170		more to 54 more)		
New or ne	wly enlarged	T2 lesions (me	an number) (follow	v-up 96 weeks; Bo	etter indicated by	lower values)						
1	randomised	serious ²	no serious	no serious	serious ³	none	153	139	-	MD 9.4 lower (14.26 to		CRITICAL
	trials		inconsistency	indirectness						4.54 lower)	LOW	
GAD lesio	ns (mean nur	nber) (follow-u	ıp 96 weeks; Better	indicated by low	er values)					·		
1	randomised	serious ²	no serious	no serious	serious ³	none	161	144	-	MD 1.3 lower (2.26 to 0.34		CRITICAL
	trials		inconsistency	indirectness						lower)	LOW	
Relapse fr	ee (number o	f participants)	(follow-up 128 we	eks)								
1	randomised	serious ⁴	no serious	no serious	serious ³	none	42/125	31/126	RR 1.37 (0.92	91 more per 1000 (from 20		CRITICAL
	trials		inconsistency	indirectness			(33.6%)	(24.6%)		fewer to 251 more)	LOW	
								1	1	91 more per 1000 (from 20		
								24.6%		fewer to 251 more)		
Disability	progression (number of par	ticipants worsened	(follow-up 128	weeks)				L	,		
1	randomised	serious ⁴	no serious	no serious	serious ³	none	29/125	37/126	RR 0.79 (0.52	62 fewer per 1000 (from		CRITICAL
	trials	50110 415	inconsistency	indirectness	50110 415		(23.2%)	(29.4%)	to 1.2)	141 fewer to 59 more)	LOW	GIGITOTIE
									<u> </u>	62 fewer per 1000 (from		
								29.4%		141 fewer to 59 more)		
Discontinu	uation due to	anv reason (fol	llow-up 128 weeks)									
	randomised	serious ⁴	no serious	no serious	serious ³	none	23/125	29/126	RR 0.8 (0.49 to	46 fewer per 1000 (from		CRITICAL
	trials	Serious	inconsistency	indirectness	Serious	none	(18.4%)	(23%)	1.3)	117 fewer to 69 more)	LOW	CHITTETIE
							,		<u> </u>	46 fewer per 1000 (from		
								23%		117 fewer to 69 more)		
Cumulativ	ve gad-e T1 le	sions at month	s 6 and 12 (mean)	(follow-up 52 wee	ks: Better indica	ted by lower values)		L	, ,		
	randomised	no serious risk	` `	no serious	no serious	none	884	441	_	MD 0.73 lower (1.15 to		CRITICAL
	trials	of bias	inconsistency	indirectness	imprecision	none	00-1	777		0.31 lower)	HIGH	CHITICIE
		ly enlarging T	<u> </u>			eeks; Better indicate	d by lower val	nes)				
1	randomised	no serious risk		no serious	no serious	none	884	441		MD 1.94 lower (3.03 to		CRITICAL
1	trials	of bias	inconsistency	indirectness	imprecision		00-	771	_	0.85 lower)	HIGH	CRITICAL
	ļ.	1	· · · · · · · · · · · · · · · · · · ·	ļ.		Better indicated by	lower values)			0.03 10 (101)	111011	1
1 ercentag	randomised	no serious risk		no serious	no serious		840	423	1	MD 0.07 lower (0.19 lower		CRITICAL
1	randomised trials	of bias	inconsistency	indirectness	imprecision	none	040	423	_	to 0.06 higher)	HIGH	CKITICAL
								<u> </u>	L	no protocol available) (Iohnso		

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).

High risk of performance bias and attrition bias (different reasons for drop-out across groups) (Fox 2012).

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

Unclear risk of selection bias and reporting bias (no protocol available) (Johnson 1995).

3. Teriflunomide compared with placebo

			Quality a	assessment			No of pati	ents		Effect	Ovolity	Immontonoo
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriflunomide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse fro	ee (number of	participai	nts) (follow-up 48-1	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)		MODERATE	CRITICAL
								53%		132 more per 1000 (from 85 more to 191 more)		
Annualise			48-108 weeks; Bet	ter indicated by l	ower values)		1					
	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 1	progression (n	umber of	participants worse	ned) (follow-up 10	04-108 weeks)							
	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)	, , , , , , , , , , , , , , , , , , , ,	MODERATE	CRITICAL
								23.4%		56 fewer per 1000 (from 16 fewer to 89 fewer)		
	•		w-up 48 weeks)		<u> </u>			ı			1	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)		
Discontinu	ation due to s	ide effects	(follow-up 48-108	weeks)								
	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)		
Discontinu	ation due to a	ny reason	(follow-up 48-108	weeks)							·	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none		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 lesio	ns (estimated	mean char	nge) (Better indicat	ed by lower value	s)							
	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 lesio	n volume (cha	nge from	baseline) (Better in	dicated 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)	O O O O	CRITICAL
Patients fi	ree from enhar	nced lesion	s (follow-up 108 we	eeks)								
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)		MODERATE	CRITICAL
								39.7%		246 more per 1000 (from 155 more to 345 more)		
Risk of no	t having cance	r (number	of participants wit	th 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 inf	fection (numbe	er of partic	cipants with any inf	ection) (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)		

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

4. Dimethyl fumarate compared with placebo

			Quality ass	essment			No of pat	ients		Effect	0124	T
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dimethyl fumarate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse fi	ree (number of	f participants)	(follow-up 104 we	eks)								
2	randomised	serious1	serious ²	no serious	no serious	none	554/769	434/771		158 more per 1000 (from 79		CRITICAL
	trials			indirectness	imprecision		(72%)	(56.3%)	to 1.43)	more to 242 more)	LOW	
								56.4%		158 more per 1000 (from 79 more to 243 more)		
Annualise	ed relapse rate	(follow-up 104	weeks; Better ind	licated by lower v	alues)							
2	randomised	serious1	no serious	no serious	no serious	none	771	771	-	MD 0.19 lower (0.25 to 0.13		CRITICAL
	trials		inconsistency	indirectness	imprecision					lower)	MODERATE	
Disability	progression (1	number of part	ticipants worsened	l) (follow-up 104 v								
2	randomised	serious1	no serious	no serious	serious ³	none	112/768	172/771		76 fewer per 1000 (from 33		CRITICAL
	trials		inconsistency	indirectness			(14.6%)	(22.3%)	to 0.85)	fewer to 109 fewer)	LOW	
								22%		75 fewer per 1000 (from 33 fewer to 108 fewer)		
Discontin	uation due to s	side effects (fol	low-up 104 weeks)	,								•
2	randomised	serious ¹	no serious	no serious	serious ³	none	126/773	130/773	RR 0.97 (0.78	5 fewer per 1000 (from 37		CRITICAL
	trials		inconsistency	indirectness			(16.3%)	(16.8%)	to 1.21)	fewer to 35 more)	LOW	
										5 fewer per 1000 (from 37		
								16.7%		fewer to 35 more)		
								10.770				
Mortality	(follow-up 104	4 weeks)										
2		no serious risk	no serious	no serious	serious ³	none	0/773	1/773	RR 1 (1 to 1)	-		CRITICAL
	trials	of bias	inconsistency	indirectness			(0%)	(0.1%)			MODERATE	
			_					0.1%		-		
Discontin	uation due to a	any reason (fol	low-up 104 weeks)									
2	randomised	serious ¹	no serious	no serious	serious ³	none	170/773	176/773	RR 0.97 (0.8 to	7 fewer per 1000 (from 46		CRITICAL
	trials		inconsistency	indirectness			(22%)	(22.8%)	1.16)	fewer to 36 more)	LOW	
			_					22.90/		7 fewer per 1000 (from 46		
								22.8%		fewer to 36 more)		
GAD lesio	ons (mean nun	nber) (follow-u	p 104 weeks; Bette	er indicated by lov	wer values)							
2	randomised	serious ¹	no serious	no serious	no serious	none	299	309	-	MD 1.64 lower (2.17 to 1.1		CRITICAL
	trials		inconsistency	indirectness	imprecision					lower)	MODERATE	
New or no	ewly enlarged	T2 lesions (mea	an number) (follow	v-up 104 weeks; E	Better indicated b	y lower values)						

	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)	O O O O	CRITICAL
Risk of no	t having cance	er (number of)	participants with a	ny neoplasm) (fol	low-up 104 week	s)						
	randomised trials		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 sea	rious infection	(number of pa	rticipants with an	y infection) (follow	w-up 104 weeks)							
	randomised trials		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 inf	fection (numb	er of participa	nts with any infect	on) (follow-up 10	4 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%)	(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 a	ssessment			No of pa	tients		Effect	014-	T
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fingolimod	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse fr	ee (number of	participan	ts) (follow-up 104 v	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)		MODERATE	CRITICAL
								49.2%		216 more per 1000 (from 138 more to 310 more)		
Disability	1		participants worser				<u> </u>		T		ı	ı
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102/783 (13%)	142/773 (18.4%)	,	53 fewer per 1000 (from 18 fewer to 81 fewer)	LOW	CRITICAL
								18.3%		53 fewer per 1000 (from 18 fewer to 81 fewer)		
Annualise	d relapse rate (follow-up	104 weeks; Better	indicated by lower	values)							
2	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)	O O O O	CRITICAL
GAD lesio	ons (number of	patients w	rith no lesions) (follo	ow-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%)	,	234 more per 1000 (from 176 more to 293 more)	OODERATE	CRITICAL
								65.2%		235 more per 1000 (from 176 more to 293 more)		
New or ne	wly enlarged T	2 lesions (number of patients	with no lesions) (follow-up 104 wee	ks)						
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)	,	O O O O	CRITICAL
								23.6%		274 more per 1000 (from 182 more to 385 more)		
Discontinu	uation due to a	ny reason	(follow-up 104 weel	ks)								
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	142/783 (18.1%)	186/773 (24.1%)	,	60 fewer per 1000 (from 2 fewer to 103 fewer)	LOW	CRITICAL
								24.4%		61 fewer per 1000 (from 2 fewer to 105 fewer)		
Discontinu	uation due to si	de effects	(follow-up 104 weel	ks)								
2	randomised trials	serious ¹	serious ³	no serious indirectness	serious ²	none	123/783 (15.7%)	86/773 (11.1%)		47 more per 1000 (from 9 fewer to 130 more)	VERY LOW	CRITICAL

		1	1								1	
								11.1%		47 more per 1000 (from 9 fewer to 130 more)		
GAD lesi	ons (mean num	ber) (follow	w-up 104 weeks; Be	tter indicated by l	ower 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 n	ewly enlarged	Γ2 lesions (mean number) (foll	ow-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	n brain volume	(percent c	hange) (follow-up 1	04 weeks; Better i	ndicated 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 ca	ancer (number	of particip	ants with any neopl	asm) (follow-up 1	04 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 in	fection (number	er of partic	ipants with any infe	ection) (follow-up	104 weeks)							
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none		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 ass	essment			No of pat	ients		Effect	Ouality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Natalizumab	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Relapse fr	ee (number of	participants) ((follow-up 52 weel	ks)		•		•				•
	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 fr	ee (number of	participants) ((follow-up 104 wee	eks)								
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	
	urais	or oras	inconsistency	muncetness	Imprecision		(73.070)	,	1.01)	274 more per 1000 (from 186	mon	
								46.4%		more to 376 more)		
Cumulati	ve disability pi	ogression (nu	nber of participan	ts worsened) (foll	ow-up 104 weeks)		!	Į			ļ
1		no serious risk		no serious	serious ¹	none	106/627	91/315	RR 0.59 (0.46	118 fewer per 1000 (from 72		CRITICAL
	trials	of bias	inconsistency	indirectness			(16.9%)	(28.9%)	to 0.75)	fewer to 156 fewer)	MODERATE	
								28.9%		118 fewer per 1000 (from 72		
								20.9%		fewer to 156 fewer)		
Annualise	ed relapse rate	(follow-up 52	weeks; Better indi	cated by lower va	lues)							
1	randomised	no serious risk		no serious	no serious	none	627	315	-	MD 0.51 lower (0.67 to 0.35		CRITICAL
	trials	of bias	inconsistency	indirectness	imprecision					lower)	HIGH	
A	. 1 1	(C. II 104		P 4 - 3 b 1	-1							
Annualise	_	no serious risk	weeks; Better ind	_		L	(27	215	Ī	MD 0.5.1 (0.62.40.27		CRITICAL
1	randomised trials	no serious risk of bias	inconsistency	no serious indirectness	no serious imprecision	none	627	315	-	MD 0.5 lower (0.63 to 0.37 lower)	HIGH	CKITICAL
Discontin	1	L	low-up 52 weeks)	mancemess	imprecision					10 ((c))	mon	
1	randomised	no serious risk		no serious	serious ¹	none	15/627	6/315	RR 1.26 (0.49	5 more per 1000 (from 10		CRITICAL
	trials	of bias	inconsistency	indirectness	Serious	none	(2.4%)	(1.9%)	to 3.21)	fewer to 42 more)	MODERATE	
			-					1.00/		5 more per 1000 (from 10		
								1.9%		fewer to 42 more)		
Discontin	uation due to a	ny reason (fol	low-up 104 weeks)									
1	randomised	no serious risk	no serious	no serious	serious ¹	none	52/627		RR 0.84 (0.55	16 fewer per 1000 (from 44		CRITICAL
	trials	of bias	inconsistency	indirectness			(8.3%)	(9.8%)	to 1.29)		MODERATE	,
										16 fewer per 1000 (from 44		
								9.8%		fewer to 28 more)		
CAD logic		how) (follow w	p 52 weeks; Better	indicated by law	on volvos)							
GAD lesio	randomised	no serious risk	,	no serious	no serious	none	627	315	_	SMD 0.56 lower (0.7 to 0.42		CRITICAL
1	trials	of bias	inconsistency	indirectness	imprecision	none	027	313	_	lower)	HIGH	CKITICAL
GAD lesio	1		p 104 weeks; Bette		1 *			1				
1	randomised	no serious risk		no serious	no serious	none	627	315	_	SMD 0.43 lower (0.57 to 0.3		CRITICAL
	trials	of bias	inconsistency	indirectness	imprecision	none.	027	0.10		lower)	HIGH	
New or no	ewly enlarged	Γ2 lesions (mea	an number) (follow	v-up 52 weeks; Be	etter indicated by	lower values)		•				
1	randomised	no serious risk	no serious	no serious	no serious	none	627	315	-	MD 4.9 lower (5.96 to 3.84		CRITICAL
	trials	of bias	inconsistency	indirectness	imprecision					lower)	HIGH	
New or no			an number) (follow	<u>, , , , , , , , , , , , , , , , , , , </u>		,		1	ı			
1	randomised	no serious risk		no serious	no serious	none	627	315	-	MD 9.1 lower (10.98 to 7.22		CRITICAL
D: 1 6	trials	of bias	inconsistency	indirectness	imprecision					lower)	HIGH	
Kisk of ca	· · · · · · · · · · · · · · · · · · ·	on-event; num no serious risk	ber of participant	s with any neopla no serious	sm) (follow-up 10 serious ¹	4 weeks)	5/627	1/215	RR 1 (0.99 to	0 fewer per 1000 (from 0		CRITICAL
1.1												

	trials	of bias	inconsistency	indirectness			(0.8%)	(0.3%)	1)	fewer to 0 more)	MODERATE	
								0.3%	1	0 fewer per 1000 (from 0		
								0.5%		fewer to 0 more)		
Risk of in	fection (numbe	er of participa	nts with any infect	ion) (follow-up 10	4 weeks)							
1	randomised	no serious risk	no serious	no serious	no serious	none	527/627	215/315	RR 1.23 (1.13	157 more per 1000 (from 89		CRITICAL
	trials	of bias	inconsistency	indirectness	imprecision		(84.1%)	(68.3%)	to 1.34)	more to 232 more)	HIGH	
								68.3%		157 more per 1000 (from 89		
								08.570		more to 232 more)		
Mortality	(risk of non-e	vent)										
1	randomised	no serious risk	no serious	no serious	serious ¹	none	2/627	0/315	RR 1 (0.99 to	-		CRITICAL
	trials	of bias	inconsistency	indirectness			(0.3%)	(0%)	1)		MODERATE	
								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 ass	essment			No of par	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daclizumab	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Relapse fr	ee (number of	participants) (follow-up 52 week	s)								
	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 (n	number of part	icipants worsened	(follow-up 52 we	eks)							
	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)		
Annualise	d relapse rate	(follow-up 52 v	weeks; Better indic	ated by lower val	ues)							
		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
Discontinu	ation due to a	ny reason										
1		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)		
Discontinu	ation due to s	ide effects (foll	ow-up 52 weeks)									
		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 atro	phy (% chang	ge in whole bra	in volume) (follow	-up 52 weeks; Bet	ter indicated by le	ower values)						
	randomised trials		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 lesio	ns (mean num	ber) (follow-up	52 weeks; Better	indicated by lowe	er values)							
	randomised trials		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 ne	wly enlarged T	Γ2 lesions (mea	n number) (follow	-up 52 weeks; Be	tter indicated by l	ower values)						
	randomised trials		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 ma	alignancy (risk	of non-event;	number of partici	pants with any ne	oplasm) (follow-u	p 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		
								0.570		fewer to 0 more)		
Risk of in	fection (numb	er of participar	nts with any infecti	on) (follow-up 52	weeks)			•				
1	randomised	no serious risk	no serious	no serious	serious ²	none	104/208	89/204	RR 1.15 (0.93	65 more per 1000 (from 31		CRITICAL
	trials	of bias	inconsistency	indirectness			(50%)	(43.6%)	to 1.41)	fewer to 179 more)	MODERATE	
								43.6%		65 more per 1000 (from 31		
								43.070		fewer to 179 more)		
Mortality	(risk of non-e	vent) (follow-u	p 52 weeks)									
1	randomised	no serious risk	no serious	no serious	serious ²	none	1/201	0/196	RR 1 (0.98 to	-		CRITICAL
	trials	of bias	inconsistency	indirectness			(0.5%)	(0%)	1.01)		MODERATE	
								0%		-	1	

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 asse	essment			No of pa	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cladribine	Placebo	Relative (95% CI)	Absolute	quanty	mportunoc
Relapse fr	ee (number of	participants) (fo	ollow-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)		
Annualise	d relapse rate (follow-up 96 w	eeks; Better indicat	ed 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
Discontinu	iation due to a	ny reason (folio	ow-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)	. ,	⊕⊕⊕O MODERATE	CRITICAL
								13.2%		37 fewer per 1000 (from 1 fewer to 62 fewer)		
Discontinu	lation due to si	ide effects (foll	ow-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%)	2.9 4)	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 an	y infection (nui	mber of particip	pants with any infec	tion) (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%)	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 sei		<u> </u>	ticipants with any i	, ,		•	T	•				
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)	,	⊕⊕⊕O MODERATE	CRITICAL
								1.8%		7 more per 1000 (from 6 fewer to 38 more)		
Risk of car	ncer (number o	of participants v	with any neoplasm)	(follow-up 96 wee								
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
B		1 1 10						0%		-		
Mortality(n			ny infection) (follow		1 10	1	1/205	0/40-	Inn a sa (a) -	1000 (6		OD/TIOA:
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%)	5.36)	0 fewer per 1000 (from 4 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
								0.5%		0 fewer per 1000 (from 4 fewer		

						1
					to 22 more)	1
					to ZZ morc)	1

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 a	ssessment			No of	f patients		Effect	0	T
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Glatiramer acetate	Relative (95% CI)	Absolute	Quality	Importance
Relapse fr	ee (number of	participa	nts) (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)	fewer to 36 more)	MODERATE	CRITICAL
								61.9%		12 fewer per 1000 (from 62 fewer to 37 more)		
Annualise			p 96-104 weeks; Be	tter 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 (r	number of	participants worse	ened) (follow-up 1	.04 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 lesio	ons (number of	patients	with no lesions) (fo	llow-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)		
								0770				
New or ne	wly enlarged	Γ2 lesions	(number of patien	ts 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 w	hite matter les	sion (mear	number) (follow-	up 104 weeks; Bet	ter indicated by	lower values)						
	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 wee	eks; Better indica	ted by lower valu	les)						

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
Combine	d active lesion	s (number	of participants fi		-up 104 weeks)		l l					
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 lesio	ons (number of	participa	nts free from) (fo	llow-up 104 week	•							
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 cort	ical lesions (m		er) (follow-up 48			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
Discontin	uation due to		1 (follow-up 208 v									
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)		
Discontin	uation due to	side effect:	s (follow-up 208 v	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)		
Discontin	uation due to	side effect:	s (follow-up 48-10	04 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)		
Discontin	uation due to	any reasoi	n (follow-up 48-10	04 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-e	event) (foll	ow-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			l .			L				· · · · · · · · · · · · · · · · · · ·		

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 performance bias. Unclear allocation concealment. High risk of missing outcome data.

10. Teriflunomide compared with interferon

			Quality asse	essment			No of pat	ients		Effect	Ouglity	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teriflunomide	Interferon	Relative (95% CI)	Absolute	Quanty	importance
Relapse fr	ee (number of)	participan	ts) (follow-up 48 we	eks)								
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)		
Annualise	d relapse rate (follow-up	48 weeks; Better inc	dicated by lower va	alues)							
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
Discontinu	ation due to si	de 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)		
Discontinu	ation due to a	ny 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 inf	ection (number	 r of partici	 pants with any infe		8 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)	to 194 more)	LOW	CRITICAL
								45.2%		36 more per 1000 (from 86 fewer to 194 more)		

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).

11. Fingolimod compared with interferon

			Quality a	assessment			No of p	atients		Effect	Ovolity	Importore
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fingolimod	Interferon	Relative (95% CI)	Absolute	Quality	Importance
Relapse fr	ee (number of	participai	nts) (follow-up 52 w	veeks)								
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 (n	umber of	participants worse	ned) (follow-up 52	2 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)		
Annualise	d relapse rate	(follow-up	52 weeks; Better i	ndicated 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)	O O O O	CRITICAL
GAD lesio	ons (number of	patients v	vith no lesions) (fol	low-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 ne	wly enlarged T	Γ2 lesions ((number of patients	s with no lesions)	(follow-up 52 weel	ks)						
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)		
Discontin	uation due to s	ide effects	(follow-up 52 week	(s)				•				
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)		
Discontin		T .	(follow-up 52 week	1		_					ı	
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

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.

	trials		inconsistency	indirectness			(7.2%)	(10.4%)	to 1.07)	fewer to 7 more)	LOW	
								10.4%		32 fewer per 1000 (from 57		
								10.470		fewer to 7 more)		
GAD lesio	ns (mean num	ber) (Bette	er indicated by low	er values)								
1	randomised	serious1	no serious	no serious	serious ³	none	374	354	-	MD 0.28 lower (0.5 to 0.06		CRITICAL
	trials		inconsistency	indirectness						lower)	LOW	
New or ne	wly enlarged T	Γ2 lesions	(mean number) (fol	low-up 52 weeks;	Better indicated b	y lower values)		•				
1	randomised	serious1	no serious	no serious	serious ³	none	372	361	-	MD 0.9 lower (1.62 to 0.18		CRITICAL
	trials		inconsistency	indirectness						lower)	LOW	
Risk of no	t having cance	r (number	of participants wit	h any neoplasm)	(follow-up 52 weel	ks)		•				
1	randomised	serious1	no serious	no serious	serious ²	none	0/429	0/431	RR 1 (1 to 1)	-		CRITICAL
	trials		inconsistency	indirectness			(0%)	(0%)			LOW	
								0%		-		
Risk of inf	ection (numbe	er of partic	cipants with any inf	ection) (follow-up	52 weeks)							
1	randomised	serious1	no serious	no serious	serious ²	none	184/429	184/431	RR 1 (0.86 to	0 fewer per 1000 (from 60		CRITICAL
	trials		inconsistency	indirectness			(42.9%)	(42.7%)	1.17)	fewer to 73 more)	LOW	
								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 a	assessment			No of pa	atients		Effect	0	T
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daclizumab	Interferon	Relative (95% CI)	Absolute	Quality	Importance
Relapse fi	ree (number of	f participai	nts) (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 (1	number of	participants worse	ened) (follow-up 1	44 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)		
Annualise	ed relapse rate	(follow-up	144 weeks; Better	indicated by low	er 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
Discontin	uation due to s	side effects	(follow-up 144 we	eks)								
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)		
Discontin	uation due to a	any reason	(follow-up 144 we	eks)				•				,
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)	O O O O	CRITICAL
								24.7%		35 fewer per 1000 (from 67 fewer to 2 more)		
New or no	ewly enlarged	T2 lesions	(mean number) (B	etter 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)	O O O O	CRITICAL
Risk of ca	ncer (risk of n	on-event;	number of particip	ants with any neo	pplasm) (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 in	fection (numb	er of partic	cipants with any in	fection) (follow-u	p 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-ev	vent) (follo	w-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)		

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

13. Alemtuzumab compared with interferon

			Quality ass	essment			No of pat	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alemtuzumab	Interferon	Relative (95% CI)	Absolute	Quality	Importance
Relapse fi	ree (number o	f participants	relapse free) (follo	ow-up 104-156 we	eeks)							
3	randomised	serious ¹	no serious	no serious	no serious	none	657/914	261/500	RR 1.38 (1.26	198 more per 1000 (from		CRITICAL
	trials		inconsistency	indirectness	imprecision		(71.9%)	(52.2%)	to 1.51)	,	MODERATE	
								51.4%		195 more per 1000 (from 134 more to 262 more)		
Relapse fi	ree (number o	f participants	relapse free) (follo	ow-up 260 weeks)						,		
1	randomised	serious ²	no serious	no serious	serious ³	none	76/112	45/111	RR 1.67 (1.29	272 more per 1000 (from		CRITICAL
	trials		inconsistency	indirectness			(67.9%)	(40.5%)	to 2.17)	118 more to 474 more)	LOW	
								40.5%		271 more per 1000 (from		
								40.570		117 more to 474 more)		
Annualise	-		4-156 weeks; Bett			T					T	
2	randomised trials	serious ¹	no serious	no serious	no serious	none	538	313	-	MD 0.25 lower (0.33 to	MODERATE	CRITICAL
A		(falla 20	inconsistency	indirectness	imprecision					0.18 lower)	MODERATE	
Annualise	randomised	serious ²	0 weeks; Better in	no serious	serious ³	none	112	111	_	MD 0.23 lower (0.3 to 0.16		CRITICAL
1	trials	serious	inconsistency	indirectness	serious	none	112	111	-	lower)	LOW	CKITICAL
Disability		number of par	rticipants worsene		1-156 weeks)					10 11 01)	20 ,,	
3	randomised	serious ¹	no serious	no serious	serious ³	none	92/914	84/500	RR 0.59 (0.4 to	69 fewer per 1000 (from 24	0000	CRITICAL
	trials		inconsistency	indirectness			(10.1%)	(16.8%)	0.86)	fewer to 101 fewer)	LOW	
								19.8%		81 fewer per 1000 (from 28		
								19.070		fewer to 119 fewer)		
Disability			rticipants worsene								T	
1	randomised	serious ²	no serious	no serious	serious ³	none	13/112	30/111	RR 0.43 (0.24	154 fewer per 1000 (from		CRITICAL
	trials		inconsistency	indirectness			(11.6%)	(27%)	to 0.78)	59 fewer to 205 fewer)	LOW	
								27%		154 fewer per 1000 (from 59 fewer to 205 fewer)		
T2 Lesion	s (number of	narticinants) (follow-up 104 wee	oke)						3) lewer to 203 lewer)		
2	randomised	serious ¹	no serious	no serious	no serious	none	362/779	226/374	RR 0.77 (0.6 to	139 fewer per 1000 (from		CRITICAL
_	trials	50110 415	inconsistency	indirectness	imprecision		(46.5%)	(60.4%)	1)	242 fewer to 0 more)	MODERATE	1
			_					(0.40/		139 fewer per 1000 (from		
								60.4%		242 fewer to 0 more)		
Discontin	uation due to	side effects (fo	llow-up 104-156 v	veeks)								
3	randomised	serious ¹	no serious	no serious	serious ³	none	21/919	39/496		54 fewer per 1000 (from 35		CRITICAL
	trials		inconsistency	indirectness			(2.3%)	(7.9%)	to 0.55)	fewer to 65 fewer)	LOW	
								7.4%		51 fewer per 1000 (from 33 fewer to 61 fewer)		

Discontir	nuation due to	side effects (f	ollow-up 260 week	s)								
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)	fewer to 114 fewer)	LOW	CRITICAL
								13.1%		85 fewer per 1000 (from 7 fewer to 114 fewer)		
Discontir	nuation due to	any reason (f	Collow-up 104-156 v	veeks)								
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 pa	articipants wi	ith any infection) (f	ollow-up 104-15	66 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%	1	149 more per 1000 (from 47 more to 271 more)		
Infection	(number of pa	articipants wi	ith any infection) (f	follow-up 260 w	eeks)					,		
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	y (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
	(0.5)							0%		-		
Mortality	y (follow-up 26	1	Т.	T .	1 . 2	T	1		T = = ==		T	T
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)		MODERATE	CRITICAL
								0.9%		0 fewer per 1000 (from 0 fewer to 0 more)		
Autoimn	nune disorders	(number of p	participants with a	ny disorder) (10	4-156 weeks' follo	w-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%	1	-		
Autoimn	une disorders	(number of p	participants with a	ny disorder) (fol	low-up 260 weeks	s)					•	•
1	randomised	no serious	no serious	no serious	serious ³	none	2/108	1/107	RR 1.98 (0.18	9 more per 1000 (from 8		CRITICAL
	trials	risk of bias	inconsistency	indirectness			(1.9%)	(0.9%)	to 21.53)	fewer to 192 more) 9 more per 1000 (from 7	MODERATE	E .
								0.9%		fewer to 185 more)		
Malignar	ncy (number o	f 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)	O O O O	CRITICAL
							(3/0)	0.9%	-	0 more per 1000 (from 15		

		fewer to 15 more)	
		icwei to 13 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"

14. Ocrelizumab compared with interferon

			Quality :	assessment			No of pa	ntients		Effect	014	T
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ocrelizumab	Interferon	Relative (95% CI)	Absolute	- Quality	Importance
Disability	improvement	(confirme	d at 12 weeks) (fol	low-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	(confirme	d at 24 weeks) (fol	low-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 (f	follow-up 9	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 infestation	ns (numb	er of participants)	(follow-up 096 we	eks)							
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 me	ore serious ad	verse even	t (number of parti	cipants) (follow-u	p 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 (fo	llow-up 90	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

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)

								21.4%		169 fewer per 1000 (from 150 fewer to 182 fewer)		
Mortality	(risk of non-e	vent) (follo	ow-up 96 weeks)					I		·	L	
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)		
Malignan	cies (risk of no	on-event) (follow-up 96 week	s)								
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)		
Discontin	uation due to a	adverse ev	 ents (follow-up 96	weeks)								
2	randomised	serious1	no serious	no serious	serious ²	none	29/827	64/829	RR 0.46 (0.3 to	42 fewer per 1000 (from 23		CRITICAL
	trials		inconsistency	indirectness			(3.5%)	(7.7%)	0.7)	fewer to 54 fewer)	LOW	
								7.7%		42 fewer per 1000 (from 23 fewer to 54 fewer)		
Discontin	uation due to a	any reason	(follow-up 96 wee	eks)		•		·				
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)		

15. Interferon compared with placebo for secondary progressive multiple sclerosis

		Qu	ality assessment			No of]	patients	E	ffect	Quality	Importance
No of studies			Indirectness	Imprecision	Interferon	Placebo	Relative (95% CI)	Absolute	Quanty	importance	
Disabili	ty progressio	n sustained	at 3 months (follo	ow-up 156 weel	ks)						
1	randomised no serious no serious no		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)				

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

Disabili	ty progressio	n sustained	at 6 months (fol	low-up 156 wee	eks)						
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	r of participa	nts wheelch	air bound (follo	w-up 156 weeks	s)						
1			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			free from) (follo	ow-up 156 week	•	,					
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)		
Discont	inuation due	to any reaso	on (follow-up 15	6 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)		
Discont	inuation due	to side effec	ts (follow-up 15	6 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)		
Discont	inuation of st	udy drug di	ue 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)		
Discont	inuation of st	udy drug dı	ue 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)		
Mortali	ty (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)		

Numbe	r of participa	nts free from	n new or newly e	enlarging T2 les	ion (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)		
Combin	ned unique ac	tivity (numl	ber of participan	ts 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 cer	rebral volui	ne from baseline	(follow-up 52 v	weeks; Better in	dicated by lo	wer 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 cer	rebral volui	ne from baseline	(follow-up 104	weeks; Better i	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 cer	rebral volui	ne from baseline	(follow-up 156	weeks; Better i	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
Absolut	te change in b	rain total le	sion volume from	n baseline (cm3	(follow-up 52	weeks; Bette	r indicated by l	ower values)			
1	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
Absolut	te change in b	rain total le	sion volume fron	n baseline (cm3	(follow-up 10	4 weeks; Bett	ter 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
Absolut	te change in b	rain total le	sion volume fron	n baseline (cm3	(follow-up 15	6 weeks; Bett	ter 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
Cumula	tive number	of new or e	nlarging lesions o	calculated from	baseline (follow	v-up 52 week	s; Better indica	ted by lower values)			
1	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
Cumula					baseline (follow	_		cated by lower values)			
1	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
Cumula	tive number	of new or e	nlarging lesions o	calculated from	baseline (follow	v-up 152 wee	ks; Better indic	cated by lower values)			
1	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
Numbe			played =>1 active	e lesion during	follow-up (follo	w-up 156 we	eks)				
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)		22

Qualit	Quality of life (follow-up 156 weeks; measured with: Multiple Sclerosis Quality of Life Inventory (MSQLI); Better indicated by higher values)													
1	randomised	serious9	no serious	no serious	no serious	310	304	-	MD 0.25 higher (0.16 to 0.34		CRITICAL			
	trials		inconsistency	indirectness	imprecision				higher)	MODERATE				

¹ Confidence intervals include a negligible effect and appreciable benefit

16. Mitoxantrone compared with placebo for secondary progressive multiple sclerosis

			Quality asses	ssment			No of pat	ients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mitoxantrone	Placebo	Relative (95% CI)	Absolute	- Luamiy	mportanoo
Disability p	rogression sus	tained at 3	months (follow-up 1	04 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)		
Participant:	s wheelchair bo	und (follov	v-up 104 weeks; ass	essed 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)		
Discontinua	ation due to any	reason (fo	ollow-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)		
Discontinua	ation due to sid	e effects (f	ollow-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)		

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.

Review question 3

1. Interferon vs placebo for primary progressive multiple sclerosis

			Quality assessi	ment			No of p	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Disability p	rogression co	nfirmed at 3 mo	nths (number of par	ticipants) (follow-	up 104 weeks	5)						
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 p	rogression co	nfirmed at 6 mo	nths (number of par	ticipants) (follow-	up 104 weeks	5)						
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)		
Discontinu	ation of study	drug due to any	reason (follow-up 1	04 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)		
Discontinu	ation of study	drug due to sid	e 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%		-		
Discontinu	ation due to a	ny reason (follo	w-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 (f	ollow-up 104 v	veeks)										
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)		

High risk of detection bias (Leary 2003). Unclear allocation concealment and risk of selective outcome reporting (Leary 2003).

Determine the continuous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Unclear allocation concealment

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

2. Glatiramer acetate vs placebo for primary progressive multiple sclerosis

			Quality a	nssessment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glatiramer acetate	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Disability	progression (1	number of	participants) (follo	ow-up median 150	6 weeks)							
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	248/627 (39.6%)	143/316 (45.3%)	to 1.02)		O O O O	CRITICAL
								45.3%		59 fewer per 1000 (from 113 fewer to 9 more)		
Time to d	isability progr	1	<u> </u>	1				1				
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	248/627 (39.6%)	143/316 (45.3%)	to 1.07)		MODERATE	IMPORTANT
								45.3%		45 fewer per 1000 (from 105 fewer to 23 more)		
Discontin	uation of drug	due to any	y reason (156 week	s' 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)	O O O O	IMPORTANT
								36.7%		11 fewer per 1000 (from 70 fewer to 59 more)		
Discontin	uation of drug	due to sid	e effects (follow-up	o 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-e	vent) (follo	ow-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.

3. Fingolimod vs placebo for primary progressive multiple sclerosis

			Quality asse	essment			No of pati	ients		Effect	Ouality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fingolimod P	Placebo	Relative (95% CI)	Absolute	Quanty	Importance
Disability	progression (r	number of parti	cipants) (3 criteria) (follow-up 156 v	weeks)		·					

 $^{^{2}}$ Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1	randomised	serious ¹	no serious	no serious	no serious	none	232/336	338/487		7 fewer per 1000 (from 62		CRITICAL
	trials		inconsistency	indirectness	imprecision		(69%)	(69.4%)	to 1.09)		MODERATE	
								69.4%		7 fewer per 1000 (from 62		
	1									fewer to 62 more)		
Disabilit	-		T	rion) (follow-up 1:	-		1	1	T		T	ı
L	randomised	serious ¹	no serious	no serious	no serious	none	154/336			34 fewer per 1000 (from 99	MODEDATE	CRITICAL
	trials		inconsistency	indirectness	imprecision		(45.8%)	(49.3%)	1.08)	fewer to 39 more)	MODERATE	
								49.3%		35 fewer per 1000 (from 99 fewer to 39 more)		
dissanti	unation of stud	y dwyg dyg to g	ide effects (follow	y un 156 wooleg)						lewel to 39 mole)		
iscontil	randomised	serious ¹	no serious	no serious	serious ²		52/336	26/497	DD 2 00 (1 4 to	01 1000 (6 20		IMPORTAN
	trials	serious	inconsistency	indirectness	serious	none	(15.5%)	(7.4%)	3.13)	81 more per 1000 (from 30 more to 157 more)	LOW	IMPORTAN
	urais		meonsistency	maneetiess			(13.570)		3.13)	81 more per 1000 (from 30	Low	
								7.4%		more to 158 more)		
Aortalit	v (risk of non-e	event) (follow-u	p 156 weeks)								I.	
,	randomised	serious ¹	no serious	no serious	serious ²	none	1/336	2/487	RR 1 (0.99 to	0 fewer per 1000 (from 0		IMPORTAN
	trials		inconsistency	indirectness			(0.3%)	(0.4%)	1.01)	fewer to 0 more)	LOW	
			-					0.40/	1	0 fewer per 1000 (from 0		
								0.4%		fewer to 0 more)		
Cancer (number of par	ticipants with a	ny neoplasm) (fo	llow-up 156 weeks	s)		·				·	
	randomised	serious1	no serious	no serious	serious ²	none	26/336	12/487	RR 3.14 (1.61	53 more per 1000 (from 15		IMPORTAN
	trials		inconsistency	indirectness			(7.7%)	(2.5%)	to 6.14)	more to 127 more)	LOW	
								2.5%		54 more per 1000 (from 15		
								1 2.0 / 0		more to 128 more)		
nfection		_		ollow-up 156 weel					T	T	T.	
	randomised	serious ¹	no serious	no serious	no serious	none	137/336	215/487	,	1 '		IMPORTAN
	trials		inconsistency	indirectness	imprecision		(40.8%)	(44.1%)	to 1.09)	fewer to 40 more)	MODERATE	
								44.2%		35 fewer per 1000 (from 97 fewer to 40 more)		
Discontin	nustion due to	any magan (fall	low-up 156 weeks	<i>,</i>)						lewel to 40 mole)		
ASCOUL	randomised	no serious risk		no serious	serious ²	nono	116/336	170/497	RR 0.99 (0.82	3 fewer per 1000 (from 63		IMPORTAN
	trials	of bias	inconsistency	indirectness	serious-	none	(34.5%)	(34.9%)	,	fewer to 70 more)	MODERATE	
	11415	OI DIUS	inconsistency	manconoss			(34.370)	, ,	10 1.2)	3 fewer per 1000 (from 63	ODERCTE	
								34.9%		fewer to 70 more)	ĺ	

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
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ocrelizumab	Placebo	Relative (95% CI)	Absolute		
Time to dis	ability progre	ssion (confirmed	at 12 weeks) (follow	v-up 120 weeks)								
	randomised	no serious risk		no serious	serious ¹	none	-	-	HR 0.76 (0.59	-	$\oplus \oplus \oplus O$	CRITICAL
	trials	OI DIAS	,	indirectness				0%	to 0.98)	-	MODERATE	
Time to dis	ability progre	ssion (confirmed	at 24 weeks) (follow	v-up 120 weeks)								
	randomised	no serious risk		no serious	serious1	none	-	-	HR 0.75 (0.58	-	$\oplus \oplus \oplus O$	CRITICAL
	trials	of bias	inconsistency	indirectness				0%	to 0.97)	-	MODERATE	
Discontinu	ation of drug	due to any reasor	າ (follow-up 120 wee	eks)								
1	randomised	no serious risk		no serious	serious ²	none	96/488		RR 0.6 (0.47 to	131 fewer per 1000 (from 75	$\oplus \oplus \oplus O$	CRITICAL
	trials	of bias	inconsistency	indirectness			(19.7%)	(32.8%)	0.77)		MODERATE	
								32.8%		131 fewer per 1000 (from 75 fewer to 174 fewer)		
Mortality (r	isk of non-eve	ent) (follow-up 120	0 weeks)									
	randomised	no serious risk		no serious	serious ²	none	4/486	1/239		0 fewer per 1000 (from 0 fewer		CRITICAL
	trials	of bias	inconsistency	indirectness			(0.8%)	(0.4%)	1.01)		MODERATE	
								0.4%		0 fewer per 1000 (from 0 fewer to 0 more)		
Malignanci	es - number o	f participants (fol	low-up 120 weeks)									
1	randomised	no serious risk		no serious	serious ²	none	11/486	2/239	RR 2.7 (0.6 to	14 more per 1000 (from 3	$\oplus \oplus \oplus O$	CRITICAL
	trials	of bias	inconsistency	indirectness			(2.3%)	(0.8%)	12.11)	fewer to 93 more)	MODERATE	
								0.8%		14 more per 1000 (from 3 fewer to 89 more)		
Neoplasms	(any) - numb	er of participants	(follow-up 120 wee	ks)	•						•	
	randomised	no serious risk		no serious	serious ²	none	8/486	7/239	RR 0.56 (0.21	13 fewer per 1000 (from 23	$\oplus \oplus \oplus O$	CRITICAL
	trials	of bias	inconsistency	indirectness			(1.6%)	(2.9%)	to 1.53)	fewer to 16 more)	MODERATE	
								2.9%		13 fewer per 1000 (from 23 fewer to 15 more)		
Serious ad	verse events ((at least 1) - numb	er of participants (f	ollow-up 120 wee	ks)		,			· ·	,	
1	randomised	no serious risk		no serious	serious ²	none	99/486	53/239	RR 0.92 (0.68	18 fewer per 1000 (from 71	$\oplus \oplus \ominus O$	CRITICAL
	trials	of bias	inconsistency	indirectness			(20.4%)	(22.2%)	to 1.23)	fewer to 51 more)	MODERATE	
								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.