Table 22: Clinical evidence profile: Immunomodulatory drugs (rituximab, rintatolimod, IV immunoglobulin G) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunomodulatory drugs (rituximab, rintatolimod, IV immunoglobulin G) versus placebo	Control	Relative (95% CI)	Absolute		
Quality of Life: SF36 physical composite (max % change from baseline) (follow-up 10 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	13 (rituximab)	15	-	MD 28 higher (1.56 to 54.44 higher)	⊕⊕OO LOW	CRITICAL
Quality of Life: SF36 mental composite (max % change from baseline) (follow-up 10 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	13 (rituximab)	15	-	MD 4 higher (29.52 lower to 37.52 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability: Fatigue severity scale (follow up 18 months; range of scores: 9-63; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	77 (rituximab)	74	-	MD 0.07 lower (3.21 lower to 3.07 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Fatigue/fatigability: Fatigue numeric rating scale (follow up 16-20 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	77 (rituximab)	74	-	MD 0.06 lower (0.5 lower to 0.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological status: Hamilton Depression Scale (follow-up 6 months; range of scores: 0-52; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[1]	serious[2]	none	23 (IV immunoglobulin G)	26	-	MD 1 lower (3.35 lower to 1.35 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Zung Self-Rating Depression Scale (follow-up 6 months; range of scores: 0-80; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	serious[1]	serious[2]	none	23 (IV immunoglobulin G)	26	-	MD 1 higher (5.44 lower to 7.44 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: mental health on the Medical Outcome Study Short Form (follow-up 150 days; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[2]	no serious inconsistency	serious[1]	very serious[2]	none	14 (IV immunoglobulin G)	14	-	MD 4.6 lower (16.07 lower to 6.87 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning: physical functioning on the Medical Outcome Study Short Form/SF36 (follow-up 150 days; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[1]	very serious[2]	none	14 (IV immunoglobulin G)	14	-	MD 4.2 higher (12.62 lower to 21.02 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning: physical functioning on the Medical Outcome Study Short Form/SF36 (follow-up 24 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	77 (rituximab)	74	-	MD 1.24 higher (7.38 lower to 9.86 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Physical functioning: functional level percentage (follow up 16-20 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	77 (rituximab)	74	-	MD 0.68 lower (5.9 lower to 4.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Serious Adverse Events with possible/probable relation to intervention (follow-up 42 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/117 (0.85%) (rintatolimod)	2/117 (1.7%)	RR 0.5 (0.05 to 5.44)	9 fewer per 1000 (from 16 fewer to 76 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: major adverse events (follow-up 21 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	very serious[4]	very serious[2]	none	3/15 (20%) (IV immunoglobulin G)	3/15 (20%)	RR 1 (0.24 to 4.18)	0 fewer per 1000 (from 152 fewer to 636 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: constitutional symptoms (follow-up 3 months)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[1]	serious[2]	none	56/73 (76.7%) (IV immunoglobulin G)	23/26 (88.5%)	RR 0.87 (0.72 to 1.05)	115 fewer per 1000 (from 248 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: any serious adverse events with possible/probable relation to intervention (follow up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/77 (10.4%) (rituximab)	0%	Peto OR 7.82 (1.89 to 32.35)	100 more per 1000 (from 30 more to 180 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events: any adverse events of at least moderate severity with possible/probable relation to intervention (follow up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26/77 (33.8%) (rituximab)	12/74 (16.2%)	RR 2.08 (1.14 to 3.81)	175 more per 1000 (from 23 more to 456 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: suspected unexpected adverse reactions (follow up 24 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/77 (2.6%) (rituximab)	1/74 (1.4%)	RR 1.92 (0.18 to 20.75)	12 more per 1000 (from 11 fewer to 267 more)	⊕⊕OO LOW	CRITICAL
Activity levels: mean number of steps per 24 hours (follow up 17-21 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	77 (rituximab)	74	-	MD 127 lower (1004 lower to 750 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Exercise performance measure: Treadmill exercise duration in seconds (follow-up 42 weeks; Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	100 (rintatolimod)	108	-	MD 56 higher (25.94 lower to 137.94 higher)	⊕OOO VERY LOW	CRITICAL
Return to school or work: Resumption of pre-morbid employment status (full-time) (follow-up 6 months)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[1]	no serious imprecision	none	6/23 (26.1%) (IV immunoglobulin G)	0/26 (0%)	Peto OR 10.79 (1.98 to 58.68)	260 more per 1000 (from 80 more to 450 more)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Marked reduction in symptoms and improvement in functional capacity (follow-up 6 months)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[1]	serious[2]	none	10/23 (43.5%) (IV immunoglobulin G)	3/26 (11.5%)	RR 3.77 (1.18 to 12.04)	320 more per 1000 (from 21 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments). Populations were downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[4] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments). Populations were downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature. Further downgraded for outcome indirectness (unclear if major adverse events were treatment-related)