Table 29: Clinical evidence profile: Corticosteroids (oral hydrocortisone or fludrocortisone, nasal flunisolide) versus placebo

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids (oral hydrocortisone or fludrocortisone, nasal flunisolide) versus placebo	Control	Relative (95% CI)	Absolute		
Quality of Life: SF36 physical (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 7.6 higher (5.36 lower to 20.56 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 energy or fatigue (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 2.1 higher (7.43 lower to 11.63 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 emotional wellbeing (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 3.8 higher (5.29 lower to 12.89 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 role emotional (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0 higher (14.96 lower to 14.96 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 role physical (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 11.8 lower (29.09 lower to 5.49 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 pain (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.6 lower (15.29 lower to 14.09 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF36 social (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 1.9 higher (11.06 lower to 14.86 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF36 general wellbeing (follow-up 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 3.7 lower (12.54 lower to 5.14 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: fatigue on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0 higher (1.1 lower to 1.1 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Chronic Fatigue Syndrome Severity Rating (follow-up 4-8 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[4]	Serious[3]	none	28 (nasal flunisolide)	28	-	MD 3.17 lower (7.48 lower to 1.14 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Profile of Mood States - fatigue (follow-up 11 weeks; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	no serious imprecision	none	38 (fludrocortisone)	45	-	MD 0.2 lower (3.47 lower to 3.07 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Profile of Mood States - fatigue (follow-up 12 weeks; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34 (hydrocortisone)	34	-	MD 1.8 lower (4.14 lower to 0.54 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Profile of Mood States - vigour (follow-up 11 weeks; range of scores: 0-32; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	no serious imprecision	none	38 (fludrocortisone)	45	-	MD 0.2 higher (2.56 lower to 2.96 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Profile of Mood States - vigour (follow-up 12 weeks; range of scores: 0-32; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34 (hydrocortisone)	34	-	MD 0.5 higher (1.07 lower to 2.07 higher)	⊕⊕OO LOW	CRITICAL
Fatigue: Wood Mental Fatigue Inventory (follow-up 11 weeks; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 0.8 higher (3.66 lower to 5.26 higher)	⊕OOO VERY LOW	CRITICAL
Physical function: SF36 physical function (follow-up 11 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 7.5 higher (3.2 lower to 18.2 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: SF36 mental health (follow-up 11 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 1.2 lower (8.92 lower to 6.52 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events: adverse events leading to study withdrawal (follow-up 6 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/20 (0%) (fludrocortisone)	2/20 (10%)	Peto OR 0.13 (0.01 to 2.13)	100 fewer per 1000 (from 250 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: adverse effects / adverse events (follow-up 6-11 weeks)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	27/58 (46.6%) (fludrocortisone)	36/65 (55.4%)	RR 0.86 (0.63 to 1.17)	78 fewer per 1000 (from 205 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: any adverse reaction (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	31/35 (88.6%) (hydrocortisone)	27/35 (77.1%)	RR 1.15 (0.93 to 1.43)	116 more per 1000 (from 54 fewer to 332 more)	⊕OOO VERY LOW	CRITICAL
Psychological status: Beck Depression Inventory (follow-up 11weeks; range of scores: 0-63; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 0.4 lower (3.43 lower to 2.63 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Beck Depression Inventory (follow-up 12 weeks; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34 (hydrocortisone)	34	-	MD 1.7 lower (3.9 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Profile of Mood States - anger (follow-up 12 weeks; range of scores: 0-48; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34 (hydrocortisone)	34	-	MD 0.8 lower (2.63 lower to 1.03 higher)	⊕⊕OO LOW	CRITICAL
Psychological status: Profile of Mood States - anxiety (follow-up 12 weeks; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34 (hydrocortisone)	34	-	MD 1.3 higher (0.17 lower to 2.77 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Profile of Mood States - confusion (follow-up 12 weeks; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34 (hydrocortisone)	34	-	MD 0.3 higher (1.18 lower to 1.78 higher)	⊕⊕OO LOW	CRITICAL
Psychological status: Profile of Mood States - depression (follow-up 12 weeks; range of scores: 0-60; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[1]	none	34 (hydrocortisone)	34	-	MD 1.6 lower (3.61 lower to 0.41 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Symptom checklist-90-R general sensitivity index (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34 (hydrocortisone)	34	-	MD 0 higher (0.1 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL
Psychological status: Symptom checklist-90-R positive symptom distress index (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	34 (hydrocortisone)	34	-	MD 0.1 higher (0.04 lower to 0.24 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Symptom checklist-90-R positive symptom total (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34 (hydrocortisone)	34	-	MD 0.2 lower (5.5 lower to 5.1 higher)	⊕⊕OO LOW	CRITICAL
Psychological status: Hamilton Depression Rating Scale (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32 (hydrocortisone)	33	-	MD 0.9 lower (2.55 lower to 0.75 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Positive and negative effect scale (PANAS) positive affect (follow-up 6 weeks; range of scores: 10-50; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 1 higher (3.67 lower to 5.67 higher)	⊕OOO VERY LOW	CRITICAL
Activity levels: activity scale (follow-up 12 weeks; range of scores: not reported; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34 (hydrocortisone)	34	-	MD 0.4 lower (1 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
Activity levels: distance before exhausted (ordinal scale) (follow-up 6 weeks; range of scores: 1-5; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0 higher (0.72 lower to 0.72 higher)	⊕OOO VERY LOW	CRITICAL
Activity levels: Duke Activity Status Index (follow-up 11 weeks; range of scores: 0-58.2; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 2.5 higher (1.49 lower to 6.49 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function: Reaction time (secs) (follow-up 6 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.01 lower (0.06 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function: inability to concentrate on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 0.6 lower (2.18 lower to 0.98 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function: forgetfulness on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 0.9 lower (2.45 lower to 0.65 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function: confusion on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.1 lower (1.68 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL
Pain: muscle pain on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.1 lower (1.82 lower to 1.62 higher)	⊕OOO VERY LOW	CRITICAL
Pain: joint pain on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.3 lower (2.39 lower to 1.79 higher)	⊕OOO VERY LOW	CRITICAL
Sleep quality: unrefreshing sleep on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 0.5 lower (1.68 lower to 0.68 higher)	⊕OOO VERY LOW	CRITICAL
[NASAL] Sleep quality: Functional Outcomes of Sleep Questionnaire (follow-up 4-8 weeks; range of scores: not reported; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	very serious[4]	serious[3]	none	28 (nasal flunisolide)	28	-	MD 0.89 higher (0.99 lower to 2.77 higher)	⊕OOO VERY LOW	CRITICAL
[NASAL] Sleep quality: Epworth Sleepiness Scale (follow-up 4-8 weeks; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	28 (nasal flunisolide)	28	-	MD 3.18 lower (6.57 lower to 0.21 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure: Treadmill time (mins) (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 2.6 higher (3.85 lower to 9.05 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Wellness scale (follow-up 11 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	serious[3]	none	38 (fludrocortisone)	45	-	MD 1.1 higher (3.58 lower to 5.78 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Wellness scale (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	30 (hydrocortisone)	35	-	MD 4.6higher (0.5 lower to 9.7 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Sickness Impact Profile (follow-up 12 weeks; range of scores: 0-68; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	33 (hydrocortisone)	34	-	MD 0.3 lower (3.46 lower to 2.86 higher)	⊕⊕OO LOW	CRITICAL
Symptom scales: headaches on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0 higher (1.55 lower to 1.55 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: painful lymph nodes on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (fludrocortisone)	20	-	MD 0.2 lower (2.31 lower to 1.91 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: sore throat on VAS (follow-up 6 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (fludrocortisone)	20	-	MD 0.2 lower (1.8 lower to 1.4 higher)	⊕OOO VERY LOW	CRITICAL

[1] 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
[2] The majority of the evidence included an indirect population (downgraded by one increment) downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature (original analysis); percentage of participants with PEM unclear [PEM reanalysis – see Appendix G for additional details].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1) downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis – see Appendix G for additional details]. 2) Additionally downgraded due to all participants having rhinitis (Kakumanu 2003)
[5] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1) downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis – see Appendix G for additional details]. 2) Additionally downgraded due the majority of evidence coming from a study where all participants had neurally-mediated hypotension (Rowe 2001)