National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review E: Methods for corticosteroid withdrawal

NICE guideline NG243

Evidence reviews underpinning recommendations 1.9.1 to 1.9.10 and recommendation for research 2 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question

In people at risk of adrenal insufficiency because of prolonged corticosteroid use, what is the best way to manage corticosteroid withdrawal when corticosteroids are no longer needed to control disease activity?

1.1.1. Introduction

Exogenous glucocorticoids are used for their anti-inflammatory and immunosuppressive properties across many conditions ranging from asthma, inflammatory bowel disease, polymyalgia rheumatica and organ transplantation.

Mild symptoms during withdrawal of exogenous glucocorticoids are an expected and common occurrence and generally do not indicate unmasked adrenal insufficiency. However, if there is underlying adrenal insufficiency, either owing to adrenal suppression or because of medication use or intrinsic pituitary/adrenal disease it is potentially life-threatening. The risk of adrenal suppression depends on the dose and duration of the exogenous steroid therapy, as well as individual factors.

Current practice is very variable. Some clinicians gradually reduce the exogenous glucocorticoid dose over months, to a lower than physiological dose, and then provided that the patient feels well on the low daily dose this is simply stopped. Other clinicians will perform testing to check for adequate adrenal function before stopping glucocorticoids.

This evidence review considers what is the best way to manage glucocorticoid withdrawal when glucocorticoids are no longer needed to control underlying disease activity.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: People on long term glucocorticoids including oral, inhaled, intranasal, topical, intra-articular, intra-muscular and intra-venous. Examples of populations: people with asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, polymyalgia, lupus, or multiple sclerosis The following stratifications will be applied: · Adults (aged ≥16 years) · Children aged > 5 to 16 years · Infants aged 1-5 years · Infants aged <1 year including neonates
Intervention(s)	Different methods of withdrawing glucocorticoids. For example: · Length of time at physiological doses · Speed of reduction · Tapering
Comparison(s)	Different methods of withdrawing compared to each other
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: · Health related quality of life for example EQ-5D, SF-36

	· Incidence of adrenal insufficiency · Incidence adrenal crisis · Hospital admission · Successful cessation of steroids as indicated by, for example, rate of relapse. · Adverse events – as reported
Study design	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids. For a systematic review (SR) to be included it must be conducted in line with the methodological processes described in the NICE manual. If sufficient details are provided, reviewers will either include the SR fully or use it as If insufficient RCT evidence is available for the committee to make recommendations, a search for non-randomised studies will also be conducted. The following study designs will be considered for inclusion: · Prospective or retrospective cohort studies that have conducted a multivariate analysis adjusting for at least age and sex and any of the following confounders if appropriate (e.g., combined oral contraceptives in adults only): - Oral hormone replacement therapy - Combined oral contraceptive - Oral oestrogens Published NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies.

Six randomised controlled trial studies were included in the review; [1-4, 6, 8, 9] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary (Table 3) below.

All studies were reported in adults apart from one study which looked at children (Gargiulo 2020[4]).

Population

Evidence came from a number of different populations including:

- Acute asthma exacerbation = 2 studies (Cydulka 1998[3] and Karan 2002[6])
- Multiple Sclerosis relapses = 2 studies (Bazi 202[1] and Zecca 2021[9])
- Steroid sensitive nephrotic syndrome = 1 study (Gargiulo 2021[4]).
- Myasthenia Gravis = 1 study (Sharshar 2021[8])

Interventions

Withdrawal interventions varied between the studies.

- Two studies (Cydulka, 1998[3]) and (Karan 2002[6]) compared 8-day courses of prednisolone or prednisone treatment for asthma and compared an abrupt stop to the treatment versus a slow taper.
- Two studies (Bazi 2021[1] and Zecca 2021[9]) compared 3 and 5 day courses of treatment for MS relapses with intravenous methylprednisolone (IV-MP) and compared a tapering regime with prednisone versus an abrupt stop.
- One study (Sharshar 2021[8]) compared a rapid taper of prednisone versus a slow taper in patients newly treated for Myasthenia gravis after disease control.
- One study (Gargiulo 2020[4]) compared a short versus long taper of prednisone in children treated for releases with steroid-sensitive nephrotic syndrome.

Other considerations

The committee agreed to exclude studies that did not report any adrenal insufficiency-specific outcomes as they do not directly answer our question.

Several studies did not report incidence of adrenal insufficiency or adrenal crisis. However, adverse events which could be indicative of withdrawal syndrome were reported and these outcomes were extracted.

Studies generally included small populations which ranged from 15 to 135 participants. Follow-up periods in the studies varied between the studies and ranged from 12 days to 15 months.

Many of the included studies looked at the withdrawal of oral prednisone. While this is not licenced for use in the UK the committee agreed that tapering strategies would not vary greatly so would still be relevant to our protocol. Two studies looked at short-term treatment with IV methylprednisolone which was then changed to oral prednisone in the control arm and tapered.

Indirectness

A number of outcomes in this review were downgraded for indirectness. Four studies were marked down for population indirectness. Two studies (Karan 2002[6] and Cydulka 1998[3]) excluded people who have taken long-term steroids (categorised as daily steroid use) and two studies (Bazi 2021[1] and Zecca 2021[9]) excluded patients using any corticosteroids in the last thirty days before entering the study.

See also the study selection flow chart in Appendix B, study evidence tables in Appendix C, forest plots in Appendix D, and GRADE tables in Appendix F.

1.1.4.2. Excluded studies.

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence.

Table 2: Summary of studies included in the evidence review.

Study	Intervention and comparison	Population	Outcomes	Comments
Bazi 2021[1] RCT N=80 Conducted in Iran	**Intervention:** Placebo/abrupt stop (n=40). 1 g of intravenous methylprednisolone daily for 5 days, followed by placebo using the same protocol as the prednisolone group. **Comparison:** Steroid taper (n=40). 1 g of intravenous methylprednisolone daily for 5 days, followed by prednisolone, which was administered orally starting on day 6 and concluding on day 25. The tapering dose of prednisone started at 50 mg on the first day and tapered off with a 25% decrease at a five-day interval over 20 days. Concomitant therapy: not reported	Condition: Multiple sclerosis (relapse) Stratum: adults Type of steroid: Prednisolone and IV methylprednisolone Route of administration: IV and oral Age (mean [SD]): placebo/abrupt stop 33 (6.9) years, steroid taper 33 (8.5) years	Incidence of adrenal insufficiency (reported narratively) Adverse events (nausea; fatigue) Follow up: 6 months	Indirectness: participants did not use any corticosteroids in the last thirty days before entering the study
Cydulka 1998[3] RCT N=15 Conducted in USA	**Intervention:** Prednisone 40mg/day for 8 days (no taper) (n=7) **Comparison:** 8-day tapering course of prednisone (40 mg to 0 mg) (n=8). Beginning with 40 mg/day and tapering by 5 mg/day. Patients were given eight tablets to take each day: 5-mg prednisone tablets, up to the daily dose of prednisone, plus placebo look-alike tablets comprising the remainder of the eight tablets. Concomitant therapy: not reported	Condition: Asthma (acute asthma exacerbation judged to be suitable for discharge from the emergency department) Stratum: adults Type of steroid: Prednisone Route of administration: oral Age (mean [SD]): no taper 24.1 (5) years, 8-day taper 32 (8.5) years	Incidence of adrenal suppression Follow up: 12 days	Indirectness: patients already using inhaled or oral steroids, or those requiring chronic steroid use were excluded

Study	Intervention and comparison	Population	Outcomes	Comments
Gargiulo 2021[4] RCT N=78 Conducted in Italy	**Intervention:** Short prednisone taper (n=38). The induction dose of PDN was 60 mg/m2/day with a maximum dose of 60 mg. After 5 days on remission, patients received 18 doses of 40 mg/m2 of PDN on alternate days, with a maximum dose of 50 mg. **Comparison:** Long prednisone taper (n=40). The induction dose of PDN was 60 mg/m2/day with a maximum dose of 60 mg. After 5 days on remission, the 40 mg/m2 dose was tapered over 72 days by steps of 6 doses. Concomitant therapy: All patients received a full induction dose of PDN in 2 separate daily doses until remission was achieved for 5 consecutive days. Thereafter, PDN was prescribed according to protocol, and was given as a single dose on alternate days. The total dose of PDN was the same in both arms. The dose of PDN was estimated based on weight, using published formulas. For patients treated with maintenance PDN therapy, doses were calculated in the same way regardless of the maintenance dose, which was incorporated into the same final dose for all patients. Treatment with maintenance PDN therapy allowed if the dose did not exceed 15 mg/m2 on alternate days.	Condition: Nephrotic syndrome (at least one relapse in the previous year, but remission at enrolment) Stratum: children (also included infants) Type of steroid: Prednisone Route of administration: oral Age (median [interquartile range]): short taper 7.1 (4.8 to 10.9 years), long taper 6.3 (3.9 to 8.6) years	Adverse events (symptoms that could be attributed to adrenal suppression, i.e., headache, fatigue, poor concentration, low mood, abdominal pain) Successful cessation of steroids (relapse during treatment and at 6 months; requirement for maintenance low dose PDN treatment) Follow up: 6 months	Prospective Randomized study to Optimize Prednisone therapy for relapses of Idiopathic Nephrotic syndrome in children (PROPINE)

Study	Intervention and comparison	Population	Outcomes	Comments
Karan 2002[6] RCT N=26 Conducted in India	**Intervention:** 8-day non tapering course (n=13). 40 mg/day prednisolone abruptly terminated. **Comparison:** 8-day tapering course of prednisolone (n=13). Beginning with 40mg/day and tapering by 5mg/day. Concomitant therapy: other anti-asthma medications given according to standard practice. Medications included inhaled B2-agonist, inhalational steroids and sustained release theophylline.	Condition: Asthma (acute asthma exacerbation deemed suitable for discharge) Stratum: adults Type of steroid: Prednisolone Route of administration: oral Age (mean [SD]): no taper 43.9 (12.4) years, 8-day taper 49.2 (12.1) years	Incidence of HPA axis suppression (cortisol <550nmol/L) Successful cessation of steroid (relapse rate) Follow up: 12 days	Indirectness: asthmatics already using oral steroids, or those requiring chronic steroid use were excluded
Sharshar 2021[8] RCT N=117 Conducted in France	**Intervention:** Rapid tapering (n=59). Immediate high-dose daily administration of prednisone, 0.75 mg/kg, followed by an earlier and rapid decrease once improved MG status was attained. **Comparison:** Slow tapering (n=58). Gradual increase of the prednisone dose to 1.5 mg/kg every other day and a slow decrease once minimal manifestation status of MG was attained. Concomitant therapy: In the event of an MG exacerbation, the participant was hospitalised, and the dose of prednisone was routinely doubled. In the event of a more moderate aggravation, the prednisone dose was increased to the previous dose recommended in that participant's prednisone tapering regimen.	Condition: Myasthenia Gravis Stratum: adults Type of steroid: Prednisone Route of administration: oral Age (median [interquartile range]): rapid taper 56 (18 to 80) years, slow taper 58 (22 to 81) years	Adverse events (nausea; diarrhoea; hyperkalaemia; hyponatremia) Successful cessation of steroids (attainment of minimal manifestation status without relapse or prednisolone resumption) Follow up: 15 months	Comparison of Corticosteroid Tapering Regimens in Myasthenia Gravis (MYACOR trial)

Study	Intervention and comparison	Population	Outcomes	Comments
	Azathioprine was started at 50 mg/d for 1 week, then increased by 50 mg/d weekly to a maximum dose of 3 mg/kg/d, without exceeding 200 mg/d. Azathioprine therapy was interrupted in the event of severe adverse effects and recommended to be replaced by mycophenolate mofetil. It was recommended that the oral dose of pyridostigmine did not exceed 300 mg/d. Plasmapheresis or intravenous immunoglobulin (IVIG) therapy was permitted for MG exacerbation but not for maintaining MMS.			
Zecca 2021[9] RCT N=125 Conducted in Switzerland	**Intervention:** Placebo/abrupt stop (n=13) 1,000 mg IV/day methylprednisolone for 3 consecutive days. Placebo for 25 days. **Comparison:** Steroid taper (n=12). 1,000 mg IV/day methylprednisolone for 3 consecutive days. 60 mg of oral prednisone per day for 5±2 days, and subsequently reduced the dose to 40, 20, 10, and 5 mg every 5±2 days (25 days in total). Concomitant therapy: Disease modifying therapies were continued.	Condition: Multiple sclerosis (acute relapse) Stratum: adults Type of steroid: IV methylprednisolone and Prednisolone Route of administration: IV and oral Age (median [interquartile range]): placebo 43 (35 to 54) years, steroid taper 40 (27 to 53.5) years	Adverse events (nausea; fatigue; total adverse events) Incidence of adrenal insufficiency (reported narratively as median [interquartile range] so not extractable) Follow up: 6 months	Indirectness: those with steroid treatment in the previous 30 days were excluded

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

See Appendix F for full GRADE tables.

Table 3: Clinical evidence summary: rapid tapering versus slow tapering in Myasthenia gravis

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low-tapering prednisone	Risk difference with Myasthenia gravis - Rapid-tapering prednisone
Treatment success - attainment of minimal manifestation status without prednisone treatment at 12 months and without relapse or prednisone resumption at 15 months (higher is better)	117 (1 RCT) 12 months	⊕⊕⊕◯ Moderate[a]	**RR 4.52** (1.84 to 11.09)	86 per 1,000	**303 more per 1,000** (72 more to 870 more)
Adverse events - Nausea (lower is better)	117 (1 RCT) 15 months	⊕◯◯◯ Very low[a,b]	**RR 0.98** (0.37 to 2.63)	121 per 1,000	**2 fewer per 1,000** (76 fewer to 197 more)
Adverse event - Diarrhoea (lower is better)	117 (1 RCT) 15 months	⊕◯◯◯ Very low[a,b]	**RR 2.95** (0.32 to 27.54)	17 per 1,000	**34 more per 1,000** (12 fewer to 458 more)
Adverse events – Hyperkalaemia (lower is better)	117 (1 RCT) at 15 months	⊕◯◯◯ Very low[a,b]	**RR 0.74** (0.38 to 1.42)	276 per 1,000	**72 fewer per 1,000** (171 fewer to 116 more)
Adverse events – Hyponatremia (lower is better)	117 (1 RCT) at 15 months	⊕◯◯◯ Very low[a,b]	**OR 7.26** (0.14 to 366.18	17 per 1,000	**20 more per 1,000** (30 fewer to 60 more)[c]

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to missing outcome data)
b. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8, 1.25)

c. Calculated with RD due to 0 events in one arm of a single study

Table 4: Clinical evidence summary: short taper versus long taper in steroid sensitive nephrotic syndrome

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with long taper	Risk difference with Steroid sensitive nephrotic syndrome - short taper
Successful cessation of steroids - Maintenance low dose PDN treatment required at 6 months follow-up: 6 months (higher is better)	78 (1 RCT)	⊕⊕◯◯ Low[a]	**RR 0.98** (0.53 to 1.80)	350 per 1,000	**7 fewer per 1,000** (164 fewer to 280 more)
Adverse events - Adrenal suppression specific at 6 months follow-up: 6 months (lower is better)	78 (1 RCT)	⊕⊕⊕◯ Moderate[b]	**RD 0.00** (-0.05 to 0.05)	0 per 1,000	**0 fewer per 1,000** (50 fewer to 50 more)

(a) Downgraded 2 increments as the confidence interval crossed both MIDs (0.8-1.25)
(b) Downgraded by 1 increment for imprecision due to zero events and small sample size

Table 5: Clinical evidence summary: taper after intravenous methylprednisolone compared to no taper in multiple sclerosis.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no taper after IV MP	Risk difference with taper after IV MP
Incidence of adrenal insufficiency - as reported	91 (2 RCTs) 6 months	⊕◯◯◯ Very low[a,b,c]	**RD 0.00** (-0.06 to 0.06)	0 per 1,000	**0 fewer per 1,000** (60 fewer to 60 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no taper after IV MP	Risk difference with taper after IV MP
(lower is better)					
Adverse events - Nausea (lower is better)	91 (2 RCTs) 6 months	⊕◯◯◯ Very low[a,b,d]	**RR 0.60** (0.08 to 4.26)	43 per 1,000	**17 fewer per 1,000** (40 fewer to 142 more)
Adverse events - Fatigue (lower is better)	91 (2 RCTs) 6 months	⊕◯◯◯ Very low[a,b,d]	**RR 0.42** (0.07 to 2.67)	65 per 1,000	**38 fewer per 1,000** (61 fewer to 109 more)

(a) Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to missing outcome data)
(b) Downgraded by 1 increment for population indirectness: The study excluded participants using any corticosteroids in the last thirty days before entering the study.
(c) Downgraded by 1 increment for imprecision due to zero events and small sample size.
(d) Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8-1.25)

Table 6: Clinical evidence summary: 8-day treatment with no taper vs. taper in acute asthma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with 8-day treatment no taper
Incidence of adrenal insufficiency- HPA axis suppression (lower is better)	40 (2 RCTs) 12 days	⊕◯◯◯ Very low[a,b,c,d]	**RD 0.05** (-0.11 to 0.21)	50 per 1,000	**50 fewer per 1,000** (110 fewer to 210 more)

(a) Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)
(b) Downgraded by 1 increment for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
(c) Downgraded by 1 increment for population indirectness: The study excluded patients already using oral steroids, and those requiring chronic steroid use, as defined by daily steroid use. To eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use.
(d) Downgraded by 1 increment for imprecision due to zero events and small sample size.

1.1.7. Economic evidence

1.1.7.1. Included studies.

No health economic studies were included.

1.1.7.2. Excluded studies.

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix A.

1.1.8. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9. Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 7: Unit costs

Resource	Hourly costs	Cost per minute
Band 5 Nurse	£44	£0.73
Band 6 Nurse	£54	£0.90
Band 7 Nurse	£64	£1.07
Foundation Doctor FY1	£41	£0.68
Foundation Doctor FY1	£46	£0.77
Speciality registrar	£69	£1.15
Associate specialist	£144	£2.40
Consultant medical	£153	£2.54

Source: Hospital based staff from PSSRU 2021[5], including qualification costs and excluding individual and productivity costs.

1.1.10. Evidence statements

1.1.10.1. Economic

- No relevant economic evaluations were identified.

1.2. The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

The committee included the following outcomes: health-related quality of life, incidence of adrenal insufficiency, incidence of adrenal crisis, hospital admission, successful cessation of steroids and adverse events. All outcomes have been rated as critical.

The committee agreed that outcomes reporting incidence of adrenal insufficiency/adrenal crisis or adverse events which may indicate steroid withdrawal syndrome were of particular interest. The committee decided to exclude studies that did not report any adrenal

insufficiency-related outcomes or adverse event data as these were not relevant to the research question.

The committee discussed the outcome of adverse events and agreed that this was very broad and could encompass any adverse events related to the disease activity or the study drug and not specifically related to steroid withdrawal. The committee, therefore, decided to only include outcomes that specified adrenal insufficiency as an adverse event or adverse events which could indicate steroid withdrawal syndrome or could be indicative of adrenal suppression. These included: hyperkalaemia, nausea, hyponatremia, diarrhoea, vomiting, lethargy, malaise, anorexia and myalgia.

The committee considered the outcome of the successful cessation of steroids and agreed this outcome was also very broad and should only include data which could be relevant to the research question. For example, outcomes reporting the resumption of steroids were included as the reason for this could be due to symptoms of adrenal suppression. The committee decided to exclude outcomes specifically related to the disease activity such as relapse rates.

Due to the sparsity of the evidence, the committee decided to include any length of follow-up.

The evidence available was very limited, and this was in part due to the exclusion of studies which did not report any adrenal insufficiency-related outcomes. Three of the included outcomes were reported in the evidence. Four studies directly reported the incidence of adrenal insufficiency, three studies reported successful cessation of steroids and three studies reported adrenal insufficiency-relevant adverse events.

1.2.2. The quality of the evidence

Six randomised controlled trial studies were included in the review. Withdrawal interventions varied between the studies and evidence was available for the following comparisons:

Two studies (Cydulka 1998[3]) and (Karan 2002[6]) compared 8-day courses of prednisolone or prednisone treatment for asthma and compared an abrupt stop to the treatment versus a slow taper.

Two studies (Bazi 2021[1] and Zecca 2021[9]) compared 3- and 5-day courses of treatment for MS relapses with intravenous methylprednisolone and compared a tapering regime with prednisone versus an abrupt stop.

One study (Sharshar 2021[8]) compared a rapid taper of prednisone versus a slow taper in patients newly treated for Myasthenia gravis after disease control.

One study (Gargiulo 2020[4]) compared a short versus long taper of prednisone in children treated for releases with steroid-sensitive nephrotic syndrome.

All studies were reported in adults apart from one study which looked at children (Gargiulo 2020[4]).

The evidence varied from moderate to very low quality, with the majority being of very low quality. The majority of outcomes were downgraded for risk of bias and imprecision. Risk of bias was commonly due to issues with the randomisation process, deviations from the intended interventions or missing outcome data. A number of studies did not adequately report the randomisation process or employ allocation concealment. The majority of studies had very small sample sizes, which contributed to the imprecision in the outcomes. In most cases, it was not possible to conduct a meta-analysis on outcomes as there was limited outcome data reported by the studies that was comparable enough to be meta-analysed.

Due to the sparsity of evidence available, the inclusion of indirect evidence was common. A number of outcomes in this review were downgraded for indirectness.

Four studies were marked down for population indirectness. Two studies (Karan 2002[6] and Cydulka 1998[3]) excluded people who had taken long-term steroids (categorised as daily steroid use) and two studies (Bazi 2021[1]) and Zecca 2021[9]) excluded patients using any corticosteroids in the last thirty days before entering the study. Despite these studies excluding people taking long-term steroids the committee decided to include them as indirect evidence due to the lack of available evidence.

Several studies looked at the withdrawal of oral prednisone. While this glucocorticoid is not licensed in the UK, the committee agreed that it would still be relevant to our protocol as the withdrawal strategies would be similar. Two studies looked at short-term treatment with IV methylprednisolone, which was changed to oral prednisone in the control arm and then tapered. There was no evidence available for other types of steroids or methods of administration.

The committee concluded that the evidence was very limited and of low quality. They acknowledged the effect the small sample sizes and risk of bias had on the quality rating and they also considered the influence that the indirect populations may have had on the results. The committee took this into consideration while interpreting the evidence.

1.2.3. Benefits and harms

The committee discussed the evidence available for the different corticosteroid withdrawal regimes. All outcomes were considered of equal importance at the outset. However, the committee agreed that the incidence of adrenal suppression/insufficiency was the most direct and relevant outcome for decision making. This was deemed to be of particular importance as the available studies were looking at steroid withdrawal in different populations across different conditions and were not focused on adrenal insufficiency. Consequently, when the incidence of adrenal insufficiency was reported it was the primary outcome available to answer the research question.

The outcome incidence of adrenal insufficiency was reported in four studies and assessed in two outcomes. One outcome reported the incidence of adrenal insufficiency after withdrawing from methylprednisolone for the treatment of MS relapse and showed no clinically important difference between the two tapering regimes. The other outcome reporting the incidence of adrenal insufficiency, assessed tapering after an 8-day course of prednisolone versus an abrupt stop for acute asthma. This outcome displayed a small reduction in the incidence of HPA axis suppression in the slow tapering arm, however, it only just reached the MID for clinical importance and was rated very low quality due to population indirectness, imprecision, heterogeneity, and risk of bias. Consequently, the committee did not take this finding into account in their decision making.

The committee also considered the incidence of specific adverse events that may be indicative of steroid withdrawal syndrome in their decision-making. The incidence of hyperkalaemia, hyponatraemia, nausea, fatigue, and diarrhoea were reported in the available evidence. One study reported the incidence of hyperkalaemia and hyponatremia in adults tapering prednisone after long-term treatment for myasthenia gravis. This showed a reduced incidence of hyponatremia in the slow-tapering arm but an increased incidence of hyperkalaemia. However, these outcomes were rated very low quality and reported in a very specific population so did not influence the committee's decision-making. Three studies, (assessed in 2 outcomes) reported the incidence of nausea, 2 studies reported the incidence of fatigue, and one study reported the incidence of diarrhoea, and all displayed no clinically important difference between the different tapering regimes.

While these outcomes seem to indicate that rapid tapering regimes do not lead to an increase in adverse events or incidence of adrenal insufficiency, the committee were concerned with the reporting of adrenal insufficiency-related events in the studies. It was often unclear whether these were self-reported based on symptoms or whether specific

measures such as ACTH tests were performed. Therefore, due to this uncertainty and the low quality of the evidence the committee did not take these outcomes into account in their decision-making.

The success of steroid cessation in terms of reduction of the dose without the need for resumption or maintenance dose of steroids was reported in three studies in three separate outcomes. One showed a clinically important benefit in the rapid tapering arm at 15 months while the others showed no difference. Due to the very specific population of Myasthenia Gravis, risk of bias and small sample size, the committee again did not take this into account in their decision making.

The duration, type of glucocorticoid being withdrawn, method of tapering, and the included populations varied significantly between the studies. The duration of glucocorticoid use varied from 3 days to several months, and the tapering regimes ranged from an abrupt stop to tapering over many months. The majority of evidence was on the use of oral prednisone, but it also included intravenous methylprednisolone use and prednisolone. Therefore, due to the heterogeneous nature of the evidence, the pooling of the data was not possible in the majority of cases, meaning that evidence was very limited and difficult to extrapolate to the wider population of interest.

The committee also noted that the majority of studies did not provide enough detail on how they tapered once down to the physiological dose which is the phase of tapering of particular interest to answer this research question and when adrenal insufficiency-related adverse events are most likely to occur.

Consequentially, the committee found it difficult to make recommendations and draw conclusions on steroid withdrawal regimes based on the evidence currently available and instead used their consensus opinion to formulate recommendations. They also discussed a key paper (Bel 2014[2]) that has influenced current practice and provides information on a detailed tapering schedule with the use of Mepolizumab. Unfortunately, this paper could not be included in the review as it did not compare two tapering regimes and consequently did not fit the review protocol.

The committee agreed that the heterogeneity of the available evidence represents the reality in clinical practice and that decisions around tapering are rarely straightforward and are decided on a case-by-case basis assessing the individual patient needs. The committee agreed that there is a need for additional guidance and a basic decision model for GPs and other non-specialists to assist their practice.

Consequently, they decided that a tapering regime involving taking the physiological dose every other day for 2 weeks, then taking the physiological dose twice a week for two weeks and then stopping could be trialled initially. The committee reasoned that this is roughly the equivalent to halving the dose for 2 weeks and then halving it again. They agreed that it is simple for patients to understand and follow and has been widely used in clinical practice so there should not be any safety concerns. However, they highlighted that if any symptoms of adrenal insufficiency arise or if there is any uncertainty then a specialist should be contacted.

The committee discussed that the length of time people are taking glucocorticoids must be taken into consideration and that people who have been on steroids for more than 12 weeks need particular attention. This is because, the longer the duration of suppression of hypothalamic pituitary adrenal axis, the slower the recovery is likely to be. The committee therefore stipulated that a slower tapering regimen should be considered for people who have had glucocorticoids for more than 12 weeks. For people taking prednisolone the committee discussed a simple withdrawal table developed by the Imperial Centre for Endocrinology Centre and agreed to refer to this.

The committee discussed the practice of switching to different types of glucocorticoids while tapering. They agreed that in the majority of cases, people taking a course of

dexamethasone can have the dose tapered and stopped without any issues. However, if they are taking dexamethasone for a longer duration or they encounter any difficulty while tapering then clinicians should consider switching to prednisolone. For children, hydrocortisone may be considered instead. This is due to dexamethasone being significantly more potent than prednisolone or hydrocortisone and having a longer half-life, consequently, it is difficult to give a steroid-free period over 24 hours which is not enough for the HPA axis to recover.

The committee made a strong recommendation that adults and children should not be routinely switched from prednisone to hydrocortisone when dose tapering below physiological equivalent dose as there is no evidence to support this. The committee noted this is occurring in current practice despite the lack of evidence of any clinical benefit. They explained that this could have cost implications and would require referral to endocrinology to manage the switch. In addition, the higher frequency of administration with hydrocortisone presents an increased risk to successfully adhering medication.

The committee noted that there is an increased chance of difficulties withdrawing glucocorticoids for people using multiple glucocorticoid preparations simultaneously, using high dose inhaled glucocorticoids, or for those people who received intra-articular/intra-muscular glucocorticoid injections in the previous 2 months, or receiving treatment with strong cytochrome P450 3A4 inhibitors along with glucocorticoids.

The committee concluded that there is variation in practice on how glucocorticoid medication is withdrawn when stopping treatment, and because of the lack of evidence, it is not clear which is the most effective way to do this. This can lead to inappropriate testing of adrenal function and also referrals to endocrinology. Due to the large number of people taking glucocorticoids in the UK, this may have a significant resource impact. The committee therefore decided to make a research recommendation on the best methods to manage corticosteroid withdrawal when they are no longer needed (see Appendix K).

1.2.4. Cost-effectiveness and resource use

No health economic evidence was identified for this review question, therefore, the committee made recommendations reflective of best practice.

The committee discussed resource use and costs and noted that the recommendations made were primarily concerned with providing information and advice on how to manage glucocorticoid withdrawal – and the subsequent appropriate course of action to take when adrenal insufficiency or adrenal crisis is suspected due to glucocorticoid withdrawal.

The committee noted that although this provision of additional information may cost a couple of minutes of extra staff time on top of existing appointments, the benefits of providing this information are likely to outweigh the costs due to the likelihood of this information preventing an adrenal crisis.

It was also noted that these recommendations could be associated with a cost in instances where people withdrawing from their corticosteroids do not have enough of their glucocorticoid prescription left to cover the tapering regime, doubling the physiological dose, or initiating sick-day dosing if required. The committee noted however that in instances where people do not have enough, an additional prescription is relatively cheap.

Overall, the committee considered that the recommendations generally reflect current practice. A change in practice may occur because of the recommendation to not routinely change from prednisolone to hydrocortisone to manage dose tapering below physiological equivalent dose. Stopping this occurring in practice could result in cost savings to the NHS as switching is costly both in terms of an unnecessary appointment to manage the switch and additional drug costs as hydrocortisone is more costly than prednisolone.

1.2.5. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.9.1 – 1.9.10 and a research recommendation on the best way to manage corticosteroid withdrawal when corticosteroids are no longer needed to control underlying disease activity.

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Appendices

Appendix A Review protocols

A.1 Review protocol for corticosteroid withdrawal

ID	Field	Content
1.	Review title	How to withdraw exogenous steroids
2.	Review question	3.1. In people at risk of adrenal insufficiency because of prolonged corticosteroid use, what is the best way to manage corticosteroid withdrawal when corticosteroids are no longer needed to control disease activity?
3.	Objective	To determine the efficacy and safety of different glucocorticoid withdrawal regimens.
4.	Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language studies Human studies Any search filters applied (e.g., study design) will be found in the review appendix. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).

5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: People on long term glucocorticoids including oral, inhaled, intranasal, topical, intra-articular, intra-muscular and intra-venous. Examples of populations: people with asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, polymyalgia, lupus or multiple sclerosis The following stratifications will be applied: • Adults (aged ≥16 years) • Children aged > 5 to 16 years. Infants aged 1-5 years. • Infants aged <1 year including neonates. Exclusion: None identified
7.	Intervention	Different methods of withdrawing glucocorticoids. For example: • Length of time at physiological doses • Speed of reduction • Tapering Exclusions Fludrocortisone if used on its own
8.	Comparator	Different methods of withdrawing compared to each other
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids. If insufficient RCT evidence is available for the committee to make recommendations, a search for non-randomised studies will also be conducted. The following study designs will be considered for inclusion:

		• Prospective or retrospective cohort studies that have conducted a multivariate analysis adjusting for at least age and sex and any of the following confounders if appropriate (e.g., combined oral contraceptives in adults only): - Oral hormone replacement therapy - Combined oral contraceptive. - Oral oestrogens Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Health related quality of life for example EQ-5D, SF-36 • Incidence of adrenal insufficiency • Incidence adrenal crisis • Hospital admission • Successful cessation of steroids as indicated by, for example, rate of relapse. • Adverse events – as reported. Due to the sparsity of the evidence, we will include any follow up time
13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations, and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately. • a sample of the data extractions • correct methods are used to synthesise data. • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. These will depend on the studied included in the review and may include: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Nonrandomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. For non-randomised studies, meta-analysis will be performed if more than one study reports the same combination of population, adjusted covariates and outcomes. Where this is not possible, data will be presented, and quality assessed individually per outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.

		GRADEpro will be used to assess the certainty of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ WinBUGS will be used for network meta-analysis, if possible, given the data identified.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Cystic fibrosis • Type of steroid • Route of administration • People on enzyme-inducing medications • People on enzyme- inhibiting medications	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	

20.	Anticipated or actual start date			
21.	Anticipated completion date			
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior Research Fellow] Madelaine Zucker [Technical Analyst] Alexandra Bannon [Health economist] Stephen Deed [Information specialist		

25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.	
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.	
28.	Other registration details	-	
29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	-	
32.	Details of existing review of same topic by same authors	-	
33.	Current review status	☐	Ongoing
		☐	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	-	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[7] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

	• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'. • Studies published before 2007 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[7]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Randomised controlled trials. Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Randomised controlled trials. Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 9 of 12, 26 September 2023 Cochrane Central Register of Controlled Trials to Issue 9 of 12, 26 September 2023	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 September 2023	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.

4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	Chronic Disease/ or Inflammation/ or Autoimmune Diseases/
15.	((chronic adj2 (disease* or disorder*)) or (inflammation* or "autoimmune disease*" or "autoimmune disorder*" or "auto immune disease*" or "auto immune disorder*")).ti,ab,kf.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case reports/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	exp Glucocorticoids/ or Adrenal Cortex Hormones/ or Steroids/ or Cortisone/ or exp Hydrocortisone/ or exp Corticosterone/ or Fluticasone/ or Mometasone Furoate/
38.	(corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or

	beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*).ti,ab,kf.
39.	37 or 38
40.	Substance Withdrawal Syndrome/ or Drug Tapering/
41.	(withdraw* or "with-draw*" or wean* or stop* or "step* down" or ending or taper* or termin* or sparing or discontinu* or cessation or "manag* strateg*" or eliminat*).ti,ab,kf.
42.	40 or 41
43.	36 and 39 and 42
44.	((corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*) adj3 (withdraw* or "with-draw*" or wean* or taper* or discontinu* or cessation or "manag* strateg*" or eliminat*)).ti,ab,kf.
45.	43 or 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ab.
49.	placebo.ab.
50.	randomly.ab.
51.	clinical trials as topic.sh.
52.	trial.ti.
53.	cross-over studies/
54.	(crossover or "cross over").ti,ab.
55.	or/46-54
56.	Meta-Analysis/
57.	Meta-Analysis as Topic/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	45 and (55 or 66)

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or

	hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	*chronic disease/ or *inflammation/ or *autoimmune disease/
15.	((chronic adj2 (disease* or disorder*)) or (inflammation* or "autoimmune disease*" or "autoimmune disorder*" or "auto immune disease*" or "auto immune disorder*")).ti,ab,kf.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
23.	or/17-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/25-32
34.	16 not 33
35.	limit 34 to English language
36.	exp glucocorticoid/ or *prednisolone/ or *triamcinolone/ or *methylprednisolone/ or *betamethasone/ or *corticosteroid/ or *steroid/ or *cortisone/ or *hydrocortisone/ or *corticosterone/
37.	(corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*).ti,ab,kf.

38.	36 or 37
39.	withdrawal syndrome/ or drug withdrawal/
40.	(withdraw* or "with-draw*" or wean* or stop* or "step* down" or ending or taper* or termin* or sparing or discontinu* or cessation or "manag* strateg*" or eliminat*).ti,ab,kf.
41.	39 or 40
42.	35 and 38 and 41
43.	((corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*) adj3 (withdraw* or "with-draw*" or wean* or taper* or discontinu* or cessation or "manag* strateg*" or eliminat*)).ti,ab,kf.
44.	42 or 43
45.	random*.ti,ab.
46.	factorial*.ti,ab.
47.	(crossover* or cross over*).ti,ab.
48.	((doubl* or singl*) adj blind*).ti,ab.
49.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
50.	crossover procedure/
51.	single blind procedure/
52.	randomized controlled trial/
53.	double blind procedure/
54.	or/45-53
55.	Systematic Review/
56.	Meta-Analysis/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	44 and (54 or 65)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2.	MeSH descriptor: [Adrenal Hyperplasia, Congenital] this term only
#3.	((addison* NEXT disease) or addisonian*):ti,ab,kw
#4.	((adrenal* or adrenocort* or adreno-cort*) near/3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)):ti,ab,kw
#5.	((cortisol or aldosterone or adrenocorticotrop* or adreno-corticotrop* or ACTH or (corticotropi* NEXT releas*) or (corticotrophi* NEXT releas*) or corticoliberin or CRH)

	near/3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)):ti,ab,kw
#6.	(hypoadrenal* or hypo-adrenal* or hypoadrenocorticism or "hypo adrenocorticism" or adrenoleukodystrophy or "adreno leukodystrophy" or adrenomyeloneuropathy or "adreno myeloneuropathy" or hypoaldosteronism or "hypo aldosteronism"):ti,ab,kw
#7.	((adrenogenital or "adreno genital") near/1 (syndrome or disorder*)):ti,ab,kw
#8.	((haemorrhag* or hemorrhag* or bleed*) near/3 adrenal*):ti,ab,kw
#9.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#10.	((Allgrove or 3A or TripleA or AAA) near/1 syndrome):ti,ab,kw
#11.	(CAH or "X-ALD"):ti,ab
#12.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#13.	"Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy":ti,ab,kw
#14.	MeSH descriptor: [Chronic Disease] this term only
#15.	MeSH descriptor: [Inflammation] this term only
#16.	MeSH descriptor: [Autoimmune Diseases] this term only
#17.	(((chronic or autoimmune or auto-immune) NEXT (disease* or disorder*)) or inflammation*):ti,ab,kw
#18.	(or #1-#17)
#19.	MeSH descriptor: [Adrenal Cortex Hormones] this term only
#20.	MeSH descriptor: [Glucocorticoids] explode all trees
#21.	MeSH descriptor: [Steroids] this term only
#22.	MeSH descriptor: [Cortisone] explode all trees
#23.	MeSH descriptor: [Hydrocortisone] explode all trees
#24.	MeSH descriptor: [Corticosterone] explode all trees
#25.	MeSH descriptor: [Fluticasone] this term only
#26.	MeSH descriptor: [Mometasone Furoate] this term only
#27.	(corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*):ti,ab,kw
#28.	(or #19-#27)
#29.	MeSH descriptor: [Substance Withdrawal Syndrome] this term only
#30.	MeSH descriptor: [Drug Tapering] this term only
#31.	(withdraw* or with-draw* or wean* or stop* or step-down or stepping down or ending or taper* or termin* or sparing or discontinu* or cessation or managment-strateg* or eliminat*):ti,ab,kw
#32.	(or #29-#31)
#33.	#18 and #28 and #32
#34.	((corticosteroid* or glucocorticoid* or glucocorticosteroid* or prednisone* or prednisolone* or triamcinolone* or methylprednisolone* or dexamethasone* or beclomethasone* or beclometasone* or betamethasone* or cortisone* or hydrocortisone* or fludrocortisone* or corticosterone* or steroid* or budesonide* or deflazacort* or ciclesonide* or fluticasone* or mometasone* or clobetasol* or diflucortolone* or fluocinonide* or fluocinolone*) near/3 (withdraw* or with-draw* or wean* or taper* or discontinu* or cessation or management-strateg* or eliminat*)):ti,ab,kw
#35.	#33 or #34
#36.	conference:pt or (clinicaltrials or trialsearch):so

#37.	#35 not #36

Epistemonikos search terms

1.	(title:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism" OR chronic disease* OR chronic disorder* OR inflammation* OR autoimmune disease* OR autoimmune disorder* OR auto immune disease* OR auto immune disorder*) OR abstract:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism" OR chronic disease* OR chronic disorder* OR inflammation* OR autoimmune disease* OR autoimmune disorder* OR auto immune disease* OR auto immune disorder*)) AND (title:(corticosteroid* OR glucocorticoid* OR glucocorticosteroid* OR prednisone* OR prednisolone* OR triamcinolone* OR methylprednisolone* OR dexamethasone* OR beclomethasone* OR beclometasone* OR betamethasone* OR cortisone* OR hydrocortisone* OR fludrocortisone* OR corticosterone* OR steroid* OR budesonide* OR deflazacort* OR ciclesonide* OR fluticasone* OR mometasone* OR clobetasol* OR diflucortolone* OR fluocinonide* OR fluocinolone*) OR abstract:(corticosteroid* OR glucocorticoid* OR glucocorticosteroid* OR prednisone* OR prednisolone* OR triamcinolone* OR methylprednisolone* OR dexamethasone* OR beclomethasone* OR beclometasone* OR betamethasone* OR cortisone* OR hydrocortisone* OR fludrocortisone* OR corticosterone* OR steroid* OR budesonide* OR deflazacort* OR ciclesonide* OR fluticasone* OR mometasone* OR clobetasol* OR diflucortolone* OR fluocinonide* OR fluocinolone*)) AND (title:(withdraw* OR "with-draw" OR "with-draws" OR "with-drawal" OR "with-drawn" OR wean* OR stop* OR "step down" OR "stepping down" OR ending OR taper* OR termin* OR sparing OR discontinu* OR cessation OR "management strategy" OR "management strategies" OR eliminat*) OR abstract:(withdraw* OR "with-draw" OR "with-draws" OR "with-drawal" OR "with-drawn" OR wean* OR stop* OR "step down" OR "stepping down" OR ending OR taper* OR termin* OR sparing OR discontinu* OR cessation OR "management strategy" OR "management strategies" OR eliminat*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Adrenal Insufficiency population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards.

Table 10: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.

9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Economics/
36.	Value of life/
37.	exp "Costs and Cost Analysis"/
38.	exp Economics, Hospital/
39.	exp Economics, Medical/
40.	Economics, Nursing/
41.	Economics, Pharmaceutical/
42.	exp "Fees and Charges"/
43.	exp Budgets/
44.	budget*.ti,ab.
45.	cost*.ti.
46.	(economic* or pharmaco?economic*).ti.
47.	(price* or pricing*).ti,ab.
48.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
49.	(financ* or fee or fees).ti,ab.

50.	(value adj2 (money or monetary)).ti,ab.
51.	or/35-50
52.	34 and 51
53.	limit 52 to yr="2014 -Current"

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31

33.	limit 32 to English language
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

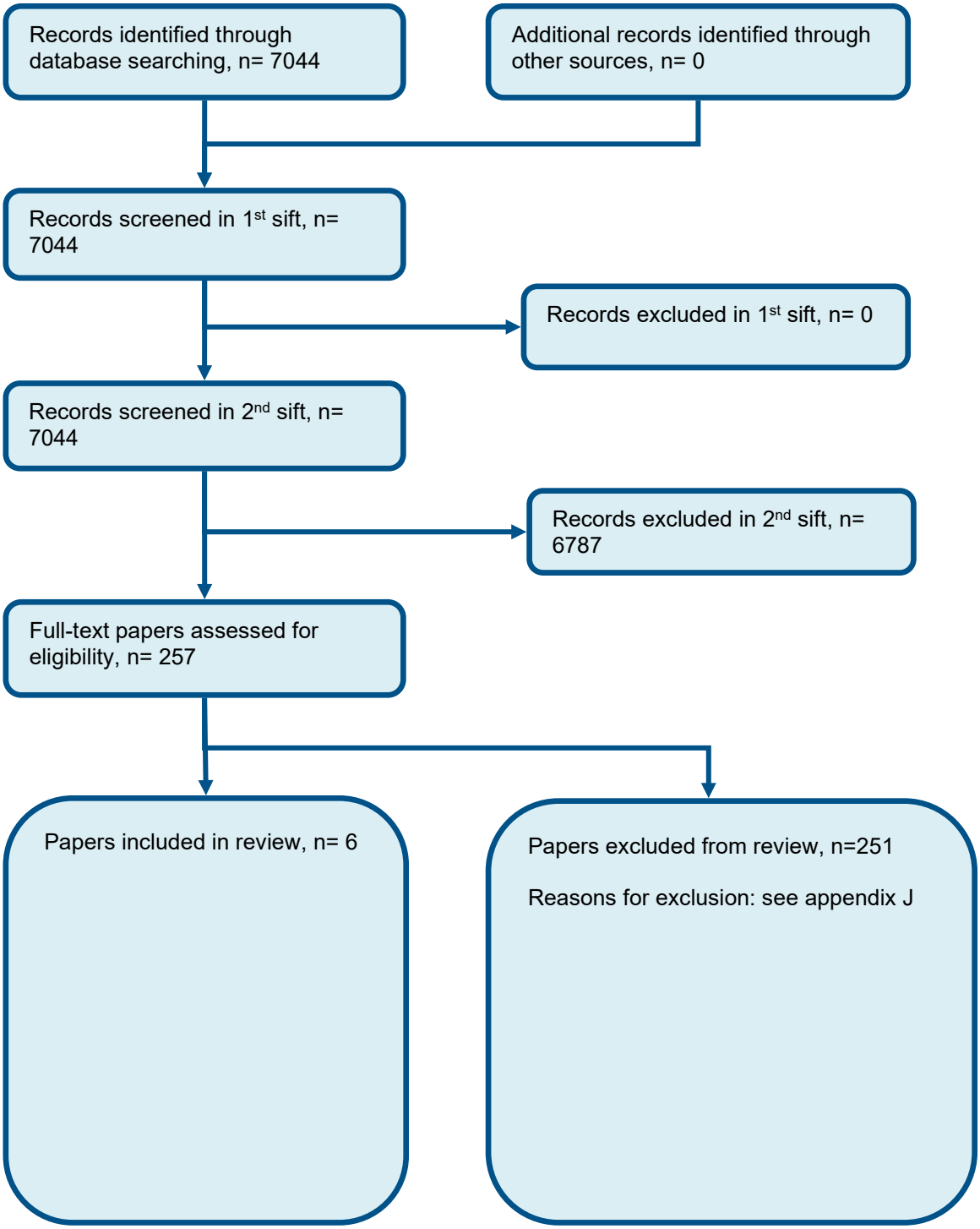
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed)
#5.	(cortisol or aldosterone or adrenocortical or adrenocorticotropi* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (insufficien* or inadequac* or deficien* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or produc* or limited)
#6.	(hypoadrenalism or hypoadrenocorticism or adrenoleukodystrophy or adrenomyeloneuropathy or hypoaldosteronism)
#7.	((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease))
#8.	(Allgrove or 3A or TripleA or AAA) AND (syndrome)
#9.	(X-ALD)
#10.	((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome))
#11.	((Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy))
#12.	(adrenogenital or adreno genital) AND (syndrome)
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

INAHTA search terms

1.	(("Adrenal Insufficiency"[mhe]) OR (hypoadrenalism) OR (addison*) OR (adrenal insufficiency) OR (adrenal crisis))

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of corticosteroid withdrawal



Appendix D Effectiveness evidence

Bazi, 2021

Bibliographic Reference	Bazi, Aliyeh; Baghbanian, Seyed Mohammad; Ghazaeian, Monireh; Saeedi, Majid; Hendoiee, Narjes; Efficacy and safety of oral prednisolone tapering following intravenous methyl prednisolone in patients with multiple sclerosis relapses: A randomized, double-blind, placebo-controlled trial.; Multiple sclerosis and related disorders; 2021; vol. 47; 102640

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	IRCT20120314009297N6
Study location	Iran
Study setting	Single centre
Study dates	October 2019 to June 2020.
Sources of funding	Supported by a grant (NO. 5163) from the Research and Technology Center of Mazandaran University of Medical Sciences, Sari, Iran.
Inclusion criteria	18–60-year-old men or women with moderate to severe MS-relapse who were treated with 1g of IVMP pulse daily for 5 days. Patients who had an Expanded Disability Status Scale (EDSS) score less than 5,1–3 months before relapse confirmation and obtained a base on pre-relapse information were in patient cases. They did not use any corticosteroids in the last thirty days before entering the study.
Exclusion criteria	Second relapse during the study or any worsening of relapse symptoms after two weeks of plus therapy that required a change in treatment; other medical conditions including pregnancy, breastfeeding, uncontrolled diabetes, and infection, hypertension, optic neuritis, neuromyelitis Optica; history of a serious adverse reaction of corticosteroids (such as gastrointestinal bleeding) or hypersensitivity to prednisolone or placebo components.
Recruitment / selection of participants	Patients presenting with MS relapse meeting the inclusion and exclusion criteria.
Intervention(s)	1 g of intravenous methylprednisolone daily for 5 days, followed by placebo using the same protocol as the prednisolone group.
Population subgroups	NA

Comparator	1 g of intravenous methylprednisolone daily for 5 days, followed by prednisolone, which was administered orally starting on day 6 and concluding on day 25. The tapering dose of prednisone started at 50 mg on the first day and tapered off with a 25% decrease at a five-day interval over 20 days.
Number of participants	80
Duration of follow-up	6 months
Indirectness	Participants did not use any corticosteroids in the last thirty days before entering the study.
Additional comments	NA

Study arms

Placebo/abrupt stop (N = 40)

1 g of intravenous methylprednisolone daily for 5 days, along with placebo.

Steroid taper (N = 40)

1 g of intravenous methylprednisolone daily for 5 days, followed by prednisolone, which was administered orally starting on day 6 and concluding on day 25. The tapering dose of prednisone started at 50 mg on the first day and tapered off with a 25% decrease at a five-day interval over 20 days.

Characteristics

Study-level characteristics

Characteristic	Study (N = 80)
Ethnicity Custom value	NR
Comorbidities Custom value	NR

Arm-level characteristics

Characteristic	Placebo/abrupt stop (N = 40)	Steroid taper (N = 40)
% Female Nominal	56.3	70.6
Mean age (SD) Mean (SD)	33 (6.9)	33 (8.5)

Outcomes

Study timepoints

- Baseline
- 6 month

Dichotomous outcomes

Outcome	Placebo/abrupt stop, Baseline, N = 40	Placebo/abrupt stop, 6 month, N = 32	Steroid taper, Baseline, N = 40	Steroid taper, 6 month, N = 34
Incidence of adrenal insufficiency as reported narratively by the study. No participants reported symptoms of AI in the ARMS questionnaire Nominal	NA	0	NA	0
Adverse events nausea Nominal	NA	0	NA	1
Adverse events fatigue Nominal	NA	1	NA	1

Incidence of adrenal insufficiency - Polarity - Lower values are better.

Adverse events - Polarity - Lower values are better.

Adverse events - Polarity - Lower values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes-Adverse Events-Nominal-Placebo/abrupt stop-Steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(The study excluded participants using any corticosteroids in the last thirty days before entering the study.)*

Dichotomous outcomes-Adverse Events-Nominal-Placebo/abrupt stop-Steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(The study excluded participants using any corticosteroids in the last thirty days before entering the study.)*

Dichotomous outcomes- Incidence of adrenal insufficiency-Nominal-Placebo/abrupt stop-Steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(The study excluded participants using any corticosteroids in the last thirty days before entering the study.)*

Cydulka, 1998

Bibliographic Reference	Cydulka, R K; Emerman, C L; A pilot study of steroid therapy after emergency department treatment of acute asthma: is a taper needed? The Journal of emergency medicine; 1998; vol. 16 (no. 1); 15-9

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	USA
Study setting	Emergency department

Study dates	NR
Sources of funding	NR
Inclusion criteria	Asthmatic patients between 19 and 50 years of age with acute asthma exacerbation presenting to the ED were eligible for entry into the study. Only those patients who were judged well enough to be discharged from the ED were recruited. Patients were judged suitable for discharge by the attending physician if they exhibited complete relief of wheezing or improvement of FEV1 to 70% predicted, or if they reported significant subjective improvement to near baseline.
Exclusion criteria	Patients with a history of chronic obstructive pulmonary disease, acute congestive heart failure, pneumonia, pneumothorax, or any other acute pulmonary disease, such as lung cancer, tuberculosis, or sarcoidosis, that might confound the results were excluded from the study. Asthmatics already using inhaled or oral steroids, those requiring chronic steroid use, as defined by daily steroid use, or those who had required steroids within 2 weeks of admission to the ED were also excluded from participating in the study. This was done to eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use, and to eliminate measurement of exogenous steroids while performing the cortisol assays. In addition, patients with a history of diabetes or severe hypertension were excluded.
Recruitment / selection of participants	Asthmatic patients between 19 and 50 years of age with acute asthma exacerbation presenting to the ED were eligible for entry into the study. Only those patients who were judged well enough to be discharged from the ED were recruited.
Intervention(s)	8-day course of 40 mg/day prednisolone (no taper). Patients who were deemed stable for discharge from the ED after three aerosolized albuterol treatments and who agreed to return on days 12 and 21 were randomized. Patients in the non-taper group were given eight 5-mg tablets to take each day.
Population subgroups	NR
Comparator	8-day tapering course of prednisolone. Patients who were deemed stable for discharge from the ED after three aerosolized albuterol treatments and who agreed to return on days 12 and 21 were randomized. 8-day tapering course of prednisolone (tapering from 40 mg to 0 mg). Beginning with 40 mg/day and tapering by 5 mg/day. Patients in the non-taper group were given eight 5-mg tablets to take each day. Patients in the taper group were given eight tablets to take each day: 5-mg prednisone tablets, up to the daily dose of prednisone, plus placebo look-alike tablets comprising the remainder of the eight tablets.
Number of participants	15
Duration of follow-up	21 days
Indirectness	Study excluded patients taking long term steroids. Asthmatics already using inhaled or oral steroids, those requiring chronic steroid use, as defined by daily steroid use, or those who had required steroids within 2 weeks of admission to the ED were also excluded from participating in the study. This was done to eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use, and to eliminate measurement of exogenous steroids while performing the cortisol assays.
Additional comments	NR

Study arms

8-day course of 40 mg/day prednisolone (no taper) (N = 7)

Patients who were deemed stable for discharge from the ED after three aerosolised albuterol treatments and who agreed to return on days 12 and 21 were randomized. Patients in the non-taper group were given eight 5-mg tablets to take each day.

8-day tapering course of prednisolone (N = 8)

Patients who were deemed stable for discharge from the ED after three aerosolised albuterol treatments and who agreed to return on days 12 and 21 were randomized. 8-day tapering course of prednisolone (tapering from 40 mg to 0 mg). Beginning with 40 mg/day and tapering by 5 mg/day. Patients in the non-taper group were given eight 5-mg tablets to take each day. Patients in the taper group were given eight tablets to take each day: 5-mg prednisone tablets, up to the daily dose of prednisone, plus placebo look-alike tablets comprising the remainder of the eight tablets.

Characteristics

Arm-level characteristics

Characteristic	8-day course of 40 mg/day prednisolone (no taper) (N = 7)	8-day tapering course of prednisolone (N = 8)
% Female Sample size	n = 2; % = 29	n = 2; % = 25
Mean age (SD) Mean (SD)	24.1 (5)	32 (8.5)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

Baseline

12 day

Dichotomous outcomes

Outcome	8-day course of 40 mg/day prednisolone (no taper), Baseline, N = 7	8-day course of 40 mg/day prednisolone (no taper), 12-day, N = 7	8-day tapering course of prednisolone, Baseline, N = 8	8-day tapering course of prednisolone, 12-day, N = 8
Incidence of adrenal suppression No of events	n = 0; % = 0	n = 0; % = 0	n = 0; % = 0	n = 0; % = 0

Incidence of adrenal suppression - Polarity - Lower values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-Incidenceofadrenalsuppression-NoOfEvents-8-day course of 40 mg/day prednisolone (no taper)-8-day tapering course of prednisolone-t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population taking chronic steroid use were excluded. - Asthmatics already using inhaled or oral steroids, those requiring chronic steroid use, as defined by daily steroid use, or those who had required steroids within 2 weeks of admission to the ED were also excluded from participating in the study. This was done to eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use, and to eliminate measurement of exogenous steroids while performing the cortisol assays)*

Gargiulo, 2021

Bibliographic Reference	Gargiulo, Antonio; Massella, Laura; Ruggiero, Barbara; Rava, Lucilla; Ciofi Degli Atti, Marta; Materassi, Marco; Lugani, Francesca; Benetti, Elisa; Morello, William; Molino, Daniela; Mattozzi, Francesca; Pennesi, Marco; Maringhini, Silvio; Pasini, Andrea;

Gianoglio, Bruno; Pecoraro, Carmine; Montini, Giovanni; Murer, Luisa; Ghiggeri, Gian Marco; Romagnani, Paola; Vivarelli, Marina; Emma, Francesco; Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children.; Kidney international; 2021; vol. 99 (no. 2); 475-483

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NR
Trial name / registration number	PROPINE - 2012-004326-16
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	10 Italian pediatric nephrology units
Study dates	March 2013 to November 2016
Sources of funding	This study was supported by a grant from the independent research on drugs program of the Italian Medicines Agency (AIFA: Agenzia Italiana del Farmaco; grant n———— FARM93J3CJ).
Inclusion criteria	Inclusion criteria included the following: age 3–17 years, at least one relapse of NS in the previous year, normal renal function (creatinine clearance >90 ml/min per 1.73 m2), remission of NS at enrolment.
Exclusion criteria	Patients were excluded if they had comorbidities not related to their NS, if they had achieved remission in >21 days at their last relapse, if they had relapsed in the previous year while receiving more than 30 mg/m2 of PDN on alternate days, if they were treated with immunosuppressive drugs other than PDN, or if they were treated with blood pressure medications.
Recruitment / selection of participants	Patients were enrolled from 10 Italian paediatric nephrology units between 2013 and 2018. Patients had frequently relapsing NS or steroid-dependent NS.
Intervention(s)	Short tapering arm: The induction dose of PDN was 60 mg/m2 per day with a maximum dose of 60 mg. After 5 days on remission, patients randomized in the short arm received 18 doses of 40 mg/m2 of PDN on alternate days, with a maximum dose of 50 mg. Concomitant therapy - Upon relapse, patients were randomized within 48 hours to 1 of the 2 arms. All patients received a full induction dose of PDN in 2 separate daily doses

	until remission was achieved for 5 consecutive days. Thereafter, PDN was prescribed according to protocol, and was given as a single dose on alternate days. The total dose of PDN was the same in both arms. The dose of PDN was estimated based on weight, using published formulas that approximate the dose per body surface with an average error of 3%. For patients that were treated with maintenance PDN therapy, doses were calculated in the same way regardless of the maintenance dose, which was incorporated into the same final dose for all patients. Treatment with maintenance PDN therapy was allowed if the dose did not exceed 15 mg/m2 on alternate days.
Population subgroups	NR
Comparator	Long tapering arm: The induction dose of PDN was 60 mg/m2 per day with a maximum dose of 60 mg. After 5 days on remission, patients randomized in the long arm, the 40 mg/m2 dose was tapered over 72 days by steps of 6 doses. Concomitant therapy - Upon relapse, patients were randomized within 48 hours to 1 of the 2 arms. All patients received a full induction dose of PDN in 2 separate daily doses until remission was achieved for 5 consecutive days. Thereafter, PDN was prescribed according to protocol, and was given as a single dose on alternate days. The total dose of PDN was the same in both arms. The dose of PDN was estimated based on weight, using published formulas that approximate the dose per body surface with an average error of 3%. For patients that were treated with maintenance PDN therapy, doses were calculated in the same way regardless of the maintenance dose, which was incorporated into the same final dose for all patients. Treatment with maintenance PDN therapy was allowed if the dose did not exceed 15 mg/m2 on alternate days.
Number of participants	78
Duration of follow-up	6 months
Indirectness	NR
Additional comments	Data were evaluated by intention-to-treat analysis

Study arms

Short tapering prednisone (N = 38)

Short tapering arm: The induction dose of PDN was 60 mg/m2 per day with a maximum dose of 60 mg. After 5 days on remission, patients randomized in the short arm received 18 doses of 40 mg/m2 of PDN on alternate days, with a maximum dose of 50 mg.

Long tapering arm (N = 40)

Long tapering arm: The induction dose of PDN was 60 mg/m2 per day with a maximum dose of 60 mg. After 5 days on remission, patients randomized in the long arm, the 40 mg/m2 dose was tapered over 72 days by steps of 6 doses.

Characteristics

Study-level characteristics

Characteristic	Study (N = 78)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	Short tapering prednisone (N = 38)	Long tapering arm (N = 40)
% Female Sample size	n = 14	n = 17
Mean age (SD) Median (IQR)	7.1 (4.8 to 10.9)	6.3 (3.9 to 8.6)

Outcomes

Study timepoints

- Baseline
- 6 months

Dichotomous outcomes

Outcome	Short tapering prednisone, Baseline, N = 38	Short tapering prednisone, 6-month, N = 38	Long tapering arm, Baseline, N = 40	Long tapering arm, 6-month, N = 40
Adverse events - Adrenal suppression specific Reported narratively by the study as symptoms that could be attributed to adrenal suppression (i.e., headache, fatigue, poor concentration, low mood, abdominal pain) No of events	n = NA; % = NA	n = 0; % = 0	n = NA; % = NA	n = 0; % = 0
Releapse at 6 months No of events	n = NA; % = NA	n = 16; % = 42	n = NA; % = NA	n = 23; % = 40
Relapse during treatment No of events	n = NA; % = NA	n = 0; % = 0	n = NA; % = NA	n = 7; % = 18

Outcome	Short tapering prednisone, Baseline, N = 38	Short tapering prednisone, 6-month, N = 38	Long tapering arm, Baseline, N = 40	Long tapering arm, 6-month, N = 40
Maintenance low dose PDN treatment required. No of events	n = NA; % = NA	n = 13; % = 34	n = NA; % = NA	n = 14; % = 35

Adverse events - Adrenal suppression specific - Polarity - Lower values are better.

Relapse at 6 months - Polarity - Lower values are better.

Relapse during treatment - Polarity - Lower values are better.

Maintenance low dose PDN treatment required - Polarity - Lower values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-MaintenancelowdosePDNtreatmentrequired-NoOfEvents-Short tapering prednisone-long tapering arm-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Releapseat6months-NoOfEvents-Short tapering prednisone-long tapering arm-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Adverseevents-Adrenalsupressionspecific-NoOfEvents-Short tapering prednisone-long tapering arm-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes-Relapse during treatment-No of Events-Short tapering prednisone-long tapering arm-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Karan, 2002

Bibliographic Reference	Karan, R S; Pandhi, P; Behera, D; Saily, R; Bhargava, V K; A comparison of non-tapering vs. tapering prednisolone in acute exacerbation of asthma involving use of the low-dose ACTH test.; International journal of clinical pharmacology and therapeutics; 2002; vol. 40 (no. 6); 256-62

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study location	India
Study setting	tertiary care
Study dates	NR
Sources of funding	NR
Inclusion criteria	Asthmatic patients between 16 and 70 years of age with acute asthma exacerbation. Only patients deemed well enough for discharge were recruited. Patients were deemed suitable for discharge if they exhibited complete relief of wheezing or improvement of FEV1 to ≥70% predicted of if they reported significant subjective improvement to near baseline.
Exclusion criteria	Patients with a history of chronic obstructive pulmonary disease, acute congestive heart failure, pneumonia, pneumothorax or any other acute pulmonary disease, such as lung cancer tuberculosis, sarcoidosis etc. that might confound the results of the study. Also excluded were asthmatics already using oral steroids, those requiring chronic steroid use, as defined by daily steroid use of those who had required steroids within 2 weeks of admission to the chest clinic. this was done to eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use. Patients with a history of diabetes or secondary hypertension were excluded.
Recruitment / selection of participants	Patients presenting to the chest clinic of PGIMER, Chandigarh who met the inclusion and exclusion criteria.

Intervention(s)	Patients who were deemed stable for discharge and who agreed to return on days 12 and 21 after discharge to the chest clinic were randomised to one of the regimes. 8-day non tapering course of 40 mg/day prednisolone abruptly terminated. Concomitant therapy- other anti-asthma medications were given according to standard practice at the PGIMER. Medications included: inhaled B2-agonist, inhalational steroids and sustained release theophylline.
Population subgroups	NR
Comparator	Patients who were deemed stable for discharge and who agreed to return on days 12 and 21 after discharge to the chest clinic were randomised to one of the regimes. 8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day. Concomitant therapy- other anti-asthma medications were given according to standard practice at the PGIMER. Medications included: inhaled B2-agonist, inhalational steroids and sustained release theophylline.
Number of participants	26
Duration of follow-up	21 days
Indirectness	Asthmatics already using oral steroids, those requiring chronic steroid use, as defined by daily steroid use of those who had required steroids within 2 weeks of admission to the chest clinic. this was done to eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use.
Additional comments	NA

Study arms

- 8-day non tapering course of 40 mg/day prednisolone abruptly terminated (N = 13)
- 8-day non tapering course of 40 mg/day prednisolone abruptly terminated
- 8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day. (N = 13)
- 8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day.

Characteristics

Study-level characteristics

Characteristic	Study (N = 26)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	8-day non tapering course of 40 mg/day prednisolone abruptly terminated (N = 13)	8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day. (N = 13)
% Female Sample size	% = 38	% = 31
Mean age (SD) Mean (SD)	43.9 (12.4)	49.2 (12.1)

Outcomes

Study timepoints

- Baseline
- 12-day

Dichotomous outcomes

Outcome	8-day non tapering course of 40 mg/day prednisolone abruptly terminated, Baseline, N = 13	8-day non tapering course of 40 mg/day prednisolone abruptly terminated, 12-day, N = 13	8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day., Baseline, N = 13	8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day., 12-day, N = 13
Incidence of HPA axis suppression Cortisol <550nmol/L) No of events	n = NA; % = NA	n = 1; % = 7.7	n = NA; % = NA	n = 0; % = 0
Successful cessation of steroid - relapse rate study reports this patient was taking long term steroids so HPA suppression may have been pre-existing. No of events	n = NA; % = NA	n = 1; % = 7.7	n = NA; % = NA	n = 0; % = 0

Incidence of HPA axis suppression - Polarity - Lower values are better.

Successful cessation of steroid - relapse rate - Polarity - Lower values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes-Successful cessation of steroid-relapse rate-No of Events- 8-day non tapering course of 40 mg/day prednisolone abruptly terminated-8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day. -t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Study excluded patients already using oral steroids, and those requiring chronic steroid use, as defined by daily steroid use. To eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use.)*

Dichotomous outcomes-Incidence of HPA axis suppression-No of Events- 8-day non tapering course of 40 mg/day prednisolone abruptly terminated-8-day tapering course of prednisolone beginning with 40mg/day and tapering by 5mg/day. -t21

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sharshar, 2021

Bibliographic Reference	Sharshar, Tarek; Porcher, Raphael; Demeret, Sophie; Tranchant, Christine; Gueguen, Antoine; Eymard, Bruno; Nadaj-Pakleza, Aleksandra; Spinazzi, Marco; Grimaldi, Lamiae; Birnbaum, Simone; Friedman, Diane; Clair, Bernard; Comparison of Corticosteroid Tapering Regimens in Myasthenia Gravis: A Randomized Clinical Trial.; JAMA neurology; 2021; vol. 78 (no. 4); 426-433

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications	NA

associated with this study included in review	
Trial name / registration number	NCT00987116. MYACOR trial
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	7 specialized centres in France
Study dates	June 2009 - February 2019
Sources of funding	Dr Tranchant reported receiving nonfinancial support from Allergan and nonfinancial support from Merz outside the submitted work. Dr Gueguen reported receiving grants from French Ministry of Social Affairs and Health during the conduct of the study; has received honoraria and consulting fees from Novartis, Roche, Merck-Serono, Sanofi-Genzyme, Teva, and Mylan; and has received travel funding from Roche, Novartis, Sanofi-Genzyme. A close relative is an Ipsen employee. No other disclosures were reported.
Inclusion criteria	Inclusion Criteria: Written consent of the patient, after informing Generalized MG of grade III, IV or V - Classification MGFA Follow-up on 15 months possible and accepted by patients
Exclusion criteria	Exclusion Criteria: Age<18 or >80 years Pregnancy Myasthenia of grade I or II of MGFA Patients already treated with prednisone or azathioprine. Contraindication for prednisone or azathioprine Other associated disease requiring a treatment with prednisone or azathioprine. Weight >100kg Invasive thymoma
Recruitment / selection of participants	NR
Intervention(s)	Initial dose - Immediately started at 0.75 mg/kg/day (without exceeding 100 mg) Intake - Daily Tapering protocol - 1) MMS reached at one month: reduction by 0.1mg/kg every 10 days to 0.45 mg/kg/day, then 0.05 mg/kg every 10 days to 0.25 mg/kg/day, then in decrements of 1 mg 2) Improved status at one month decreased by 0.1 mg/kg every 20 days until 0.45 mg/kg/day then 0.05 mg/kg every 20 days up to 0.25 mg/kg/day then 1 mg per 1 mg. If MMS is attained, then tapering is similar to the sequence 1). 3) If MMS and improvement not reached 0.75 mg/kg maintained for the first 3 months, then after decrease of 0.1 mg/kg every 20 days up to 0.45 mg/kg/day, then by 0.05 mg/kg every 20 days up to 0.25 mg/kg/day 20 days. No further reduction. If improvement is attained, the tapering follows the sequence described in 2).

	The rate of the decrease depends on the MGFA Post-intervention status attained by the patient. 1. Minimal manifestation status: decrease every 10 days from 0.75 to 0.25 mg/kg/day 2. Improved status: decrease every 20 days from 0.75 to 0.25 mg/kg/day 3. No improvement: maintenance of the dose for at most 3 months then decrease every 20 days from 0.75 to 0.25 mg/kg/day **Concomitant therapy** - Prednisone treatment was given orally and began in the hospital. On discharge from the initial hospitalisation and at the end of each monthly consultation, the necessary amount of prednisone for the following month was provided by the hospital pharmacy. The patient was asked to record the daily tablets taken in an adherence logbook and to return any tablets not taken. The tapering of the prednisone dose depended on the MGFA postintervention status in both trial groups. In the best-case scenario, prednisone would be discontinued on day 326 in the slow-tapering regimen and before day 200 in the rapid-tapering regimen in a 60-kg patient. In the event of an MG exacerbation, the participant was hospitalized, and the dose of prednisone was routinely doubled. In the event of a more moderate aggravation, the prednisone dose was increased to the previous dose recommended in that participant's prednisone tapering regimen. For both groups, azathioprine was started at 50 mg/d for 1 week, then increased by 50 mg/d weekly to a maximum dose of 3 mg/kg/d, without exceeding 200 mg/d. Azathioprine therapy was interrupted in the event of severe adverse effects and recommended to be replaced by mycophenolate mofetil. It was recommended that the oral dose of pyridostigmine did not exceed 300 mg/d. Plasmapheresis or intravenous immunoglobulin (IVIG) therapy was permitted for MG exacerbation but not for maintaining MMS.
Population subgroups	Stratified on the group of centres and thymectomy before inclusion. participants with MG duration of less than 2 years or 2 years or more at inclusion
Comparator	Initial dose - Started 10 mg, then increased by increments of 10 mg every two days up to 1.5 mg/kg (without exceeding 100 mg). Intake - Alternate days Tapering protocol - reduction by 10 mg every 2 weeks until 40 mg then reduction by 5 mg every month up to 0 mg 2) If MMS not maintained increase by 10 mg every 2 weeks until MMS, and then tapering as described. **Concomitant therapy** - Prednisone treatment was given orally and began in the hospital. On discharge from the initial hospitalisation and at the end of each monthly consultation, the necessary amount of prednisone for the following month was provided by the hospital pharmacy. The patient was asked to record the daily tablets taken in an adherence logbook and to return any tablets not taken. The tapering of the prednisone dose depended on the MGFA postintervention status in both trial groups. In the best-case scenario, prednisone would be discontinued on day 326 in the slow-tapering regimen and before day 200 in the rapid-tapering regimen in a 60-kg patient. In the event of an MG exacerbation, the participant was hospitalized, and the dose of prednisone was routinely doubled. In the event of a more moderate aggravation, the prednisone dose was increased to the previous dose recommended in that participant's prednisone tapering regimen. For both groups, azathioprine was started at 50 mg/d for 1 week, then increased by 50 mg/d weekly to a maximum dose of 3 mg/kg/d, without exceeding 200 mg/d. Azathioprine therapy was interrupted in the event of severe adverse effects and recommended to be replaced by mycophenolate mofetil. It was recommended that the oral dose of pyridostigmine did not exceed 300 mg/d. Plasmapheresis or intravenous

	immunoglobulin (IVIG) therapy was permitted for MG exacerbation but not for maintaining MMS.
Number of participants	117
Duration of follow-up	15 months
Indirectness	NA
Additional comments	The primary analysis followed the intention-to-treat principle. Accordingly, missing components for the primary outcome were handled by multiple imputation

Study arms

Rapid-tapering prednisone (N = 589)
The rapid-tapering arm consisted of immediate high-dose daily administration of prednisone, 0.75 mg/kg, followed by an earlier and rapid decrease once improved MG status was attained.

Slow-tapering prednisone (N = 58)
The slow-tapering arm included a gradual increase of the prednisone dose to 1.5 mg/kg every other day and a slow decrease once minimal manifestation status of MG was attained.

Characteristics

Study-level characteristics

Characteristic	Study (N = 117)
Ethnicity Nominal	NR

Arm-level characteristics

Characteristic	Rapid-tapering prednisone (N = 589)	Slow-tapering prednisone (N = 58)
% Female Sample size	n = 20; % = 34	n = 35; % = 60
Mean age (SD) Median (IQR)	56 (18 to 80)	58 (22 to 81)
Comorbidities Sample size	n = NA; % = NA	n = NA; % = NA
Hypertension Sample size	n = 16; % = 27	n = 11; % = 19

Characteristic	Rapid-tapering prednisone (N = 589)	Slow-tapering prednisone (N = 58)
Diabetes Sample size	n = 8; % = 14	n = 2; % = 3
osteoporosis Sample size	n = 2; % = 3	n = 4; % = 7
Psychological disorder Sample size	n = 1; % = 2	n = 1; % = 2

Outcomes

Study timepoints

- Baseline
- 15-month

Dichotomous outcomes

Outcome	Rapid-tapering prednisone, Baseline, N = 59	Rapid-tapering prednisone, 15-month, N = 59	Slow-tapering prednisone, Baseline, N = 58	Slow-tapering prednisone, 15-month, N = 58
Mortality No of events	n = NA; % = NA	n = 1; % = 2	n = NA; % = NA	n = 2; % = 3
Adverse events - Nausea No of events	n = NA; % = NA	n = 7; % = 12	n = NA; % = NA	n = 7; % = 12
Adverse event - diarrhoea No of events	n = NA; % = NA	n = 3; % = 5	n = NA; % = NA	n = 1; % = 2
Adverse events - Hyperkalaemia No of events	n = NA; % = NA	n = 12; % = 21	n = NA; % = NA	n = 16; % = 29
Adverse events - Hyponatremia No of events	n = NA; % = NA	n = 1; % = 2	n = NA; % = NA	n = 0; % = 0
Treatment success attainment of minimal manifestation status without prednisone treatment at 12 months and without relapse or prednisone resumption at 15 months No of events	n = NA; % = NA	n = 23; % = 39	n = NA; % = NA	n = 5; % = 9

Mortality - Polarity - Lower values are better.

Adverse events - Nausea - Polarity - Lower values are better.

Adverse event - diarrhoea - Polarity - Lower values are better.

Adverse events - Hyperkalaemia - Polarity - Lower values are better.

Adverse events - Hyponatremia - Polarity - Lower values are better.

Treatment success - Polarity - Higher values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes-Mortality-Nom of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes-Treatment Success-No of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes-Adverse Events-Hyponatremia-No of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes-Adverse Events-Hypokalaemia-No of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes-Adverse event-diarrhoea-No of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes – Adverse Events-Nausea-No of Events-Rapid-tapering prednisone-Slow-tapering prednisone-t15

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Zecca, 2021

Bibliographic Reference	Zecca, Chiara; Disanto, Giulio; Riccitelli, Gianna C; Candrian, Ursula; Deandrea, Maurilio; Limone, Paolo Piero; Sacco, Rosaria; Gobbi, Claudio; A randomized pilot trial of oral prednisone taper vs placebo following iv methylprednisolone for multiple sclerosis relapses: Effects on adrenal function and clinical efficacy.; Multiple sclerosis and related disorders; 2021; vol. 50; 102867

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	NR
Study dates	September 2011 to January 2015
Sources of funding	The study was funded by Advisory Board of Research Ente Ospedaliero Cantonale (ABREOC), Bellinzona, Switzerland. Liliane Petrini, Ospedale Regionale di Lugano Civico e Italiano, performed technical editing and manuscript submission.
Inclusion criteria	Inclusion criteria were age 18-80 years; Expanded Disability Status Scale (EDSS) ≤8.0; diagnosis of clinically isolated syndrome, relapsing-remitting or relapsing-progressive MS; experiencing an acute clinical relapse.

Exclusion criteria	Exclusion criteria were contraindication for steroids, MRI or gadolinium; pregnancy or breast feeding; medical or psychiatric conditions compromising the informed consent; drug abuse history during 6 months prior to screening, steroid treatment in the previous 30 days.
Recruitment / selection of participants	NR
Intervention(s)	All patients received 1,000 mg IV/day methylprednisolone for three consecutive days. Patients were randomized 1:1 to either corticosteroid (CS-GR) or placebo (PL-GR) group. PL-GR patients received placebo for 25 days. Concomitant therapy - Disease modifying therapies were continued.
Population subgroups	NR
Comparator	All patients received 1,000 mg IV/day methylprednisolone for three consecutive days. CS-GR patients received 60 mg of oral prednisone per day for 5±2 days, and subsequently reduced the dose to 40, 20, 10, and 5 mg every 5±2 days (25 days in total).
Number of participants	125
Duration of follow-up	6 months
Indirectness	NA
Additional comments	NA

Study arms

Placebo/abrupt stop (N = 13)

Steroid taper (N = 12)

Characteristics

Study-level characteristics

Characteristic	Study (N = 25)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	Placebo/abrupt stop (N = 13)	Steroid taper (N = 12)
% Female	n = 8; % = 61.5	n = 9; % = 75

Characteristic	Placebo/abrupt stop (N = 13)	Steroid taper (N = 12)
Sample size		
Mean age (SD) Median (IQR)	43 (35 to 54)	40 (27 to 53.5)

Outcomes

Study timepoints

Baseline

6-month

Dichotomous outcomes

Outcome	Placebo/abrupt stop, Baseline, N = 13	Placebo/abrupt stop, 6-month, N = 13	Steroid taper, Baseline, N = 12	Steroid taper, 6-month, N = 12
Adverse events No of events	n = NA; % = NA	n = NA; % = NA	n = NA; % = NA	n = NA; % = NA
Nausea No of events	n = NA; % = NA	n = 0; % = 0	n = NA; % = NA	n = 1
Fatigue No of events	n = NA; % = NA	n = 0; % = 0	n = NA; % = NA	n = 2
total adverse events No of events	n = NA; % = NA	n = 5	n = NA; % = NA	n = 11
Incidence of adrenal insufficiency - as reported by study reported narratively by study as data in median IQR so not extractable. No patient showed signs of adrenal insufficiency at any time by cortisol response to ACTH. No of events	n = 0; % = 0	n = 0; % = 0	n = 0; % = 0	n = 0; % = 0

Adverse events - Polarity - Lower values are better.

Incidence of adrenal insufficiency - as reported by study - Polarity - Lower values are better.

Critical appraisal - 3.1 Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomousoutcomes-Adverseevents-totaladverseevents-NoOfEvents-Placebo/abrupt stop-steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(The study excluded participants using any corticosteroids in the last thirty days before entering the study.)*

Dichotomousoutcomes-Adverseevents-Fatigue-NoOfEvents-Placebo/abrupt stop-steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Adverseevents-Nausea-NoOfEvents-Placebo/abrupt stop-steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomousoutcomes-Incidenceofadrenalinsuffiecincy-asreportedbystudy-NoOfEvents-Placebo/abrupt stop-Steroid taper-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

E.1 Rapid tapering versus slow tapering in Myasthenia gravis

Figure 2: **Successful attainment of minimal manifestation status without prednisone treatment at 12 months and without relapse or prednisone resumption at 15 months (higher is better)**

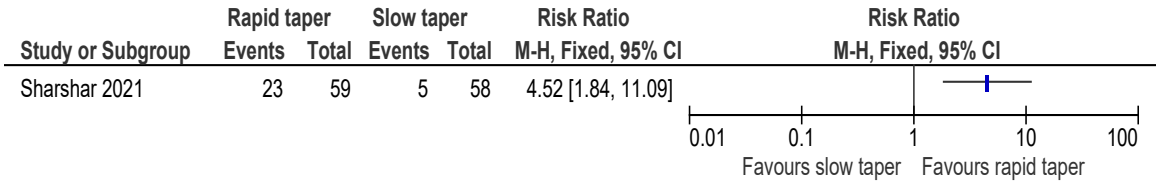


Figure 3: Adverse events - Nausea at 15 months (lower is better)

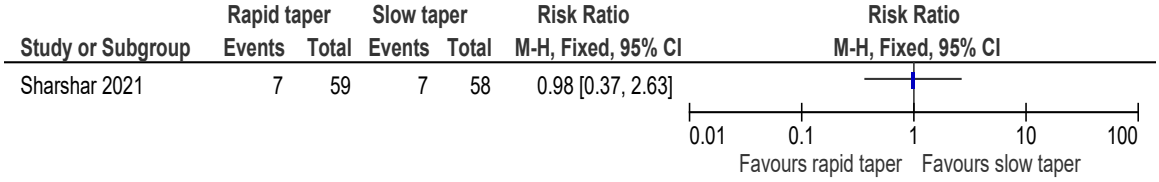


Figure 4: Adverse event - Diarrhoea at 15 months (lower is better)

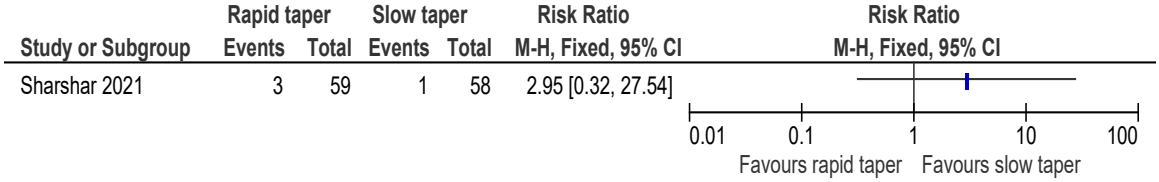


Figure 5: Adverse events - Hyperkalaemia at 15 months (lower is better)

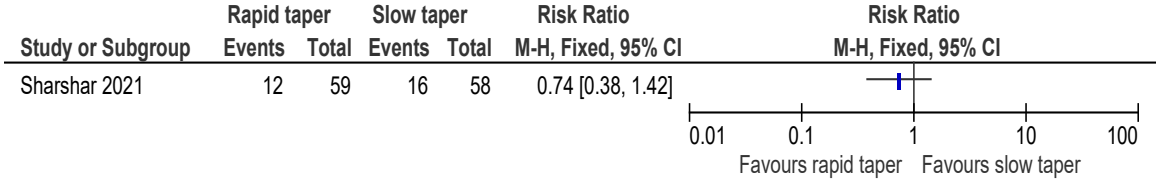
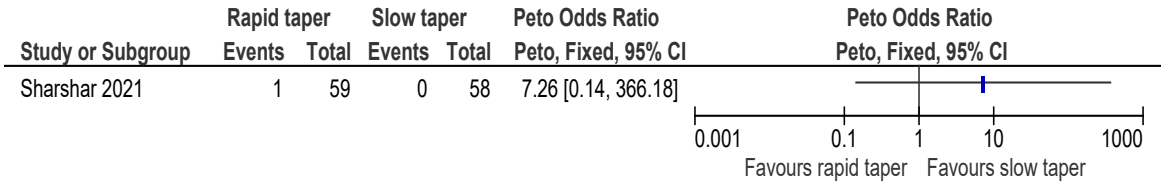


Figure 6: Adverse events - Hyponatremia at 15 months (lower is better)



E.2 Short taper versus long taper in steroid sensitive nephrotic syndrome

Figure 7: Successful cessation of steroids – Maintenance low dose PDN treatment required at 6 months (higher is better)

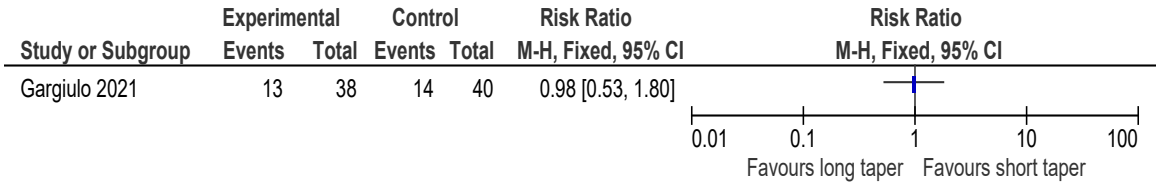
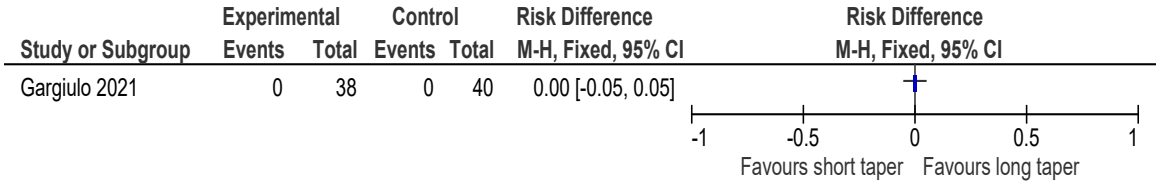


Figure 8: Adverse events - Adrenal suppression specific at 6 months (lower is better)



E.3 Taper after intravenous methylprednisolone compared to no taper in multiple sclerosis.

Figure 9: Incidence of adrenal insufficiency - as reported by study at 6 months (lower is better)s

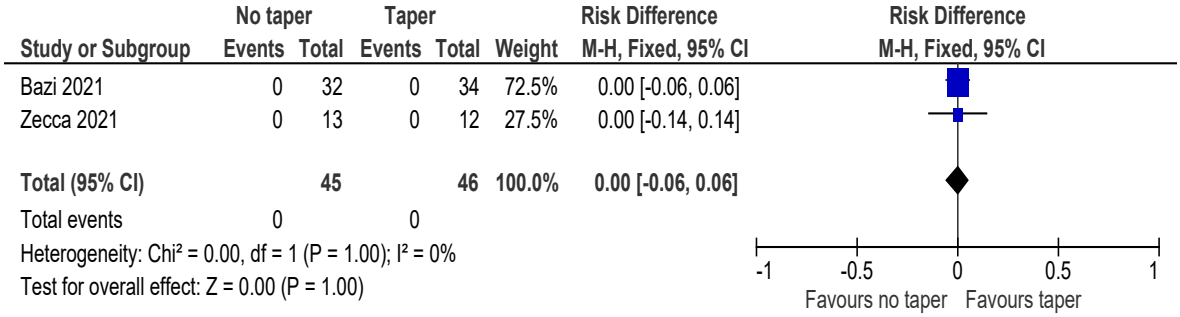


Figure 10: Adverse events - Nausea at 6 months (lower is better)

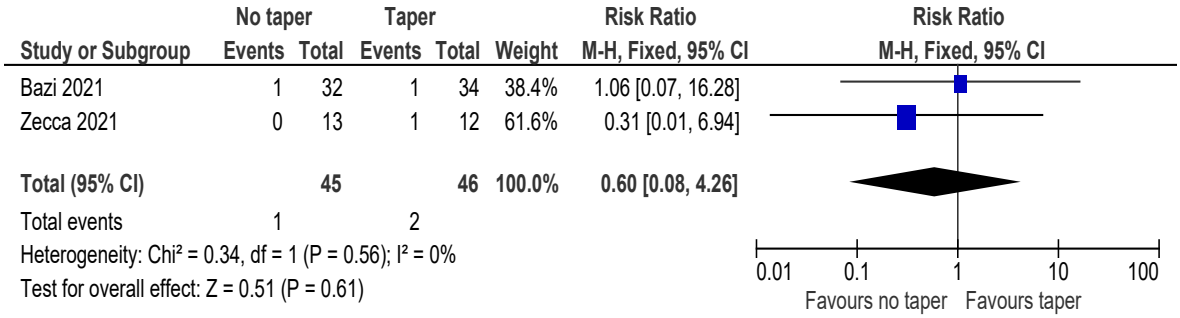
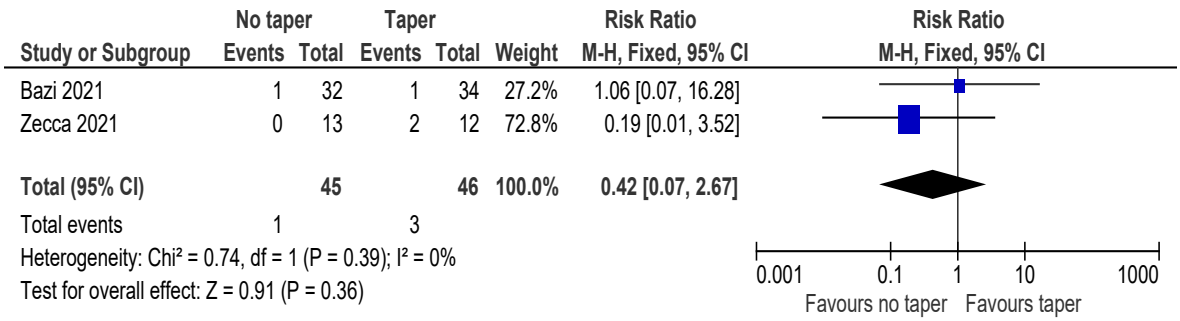
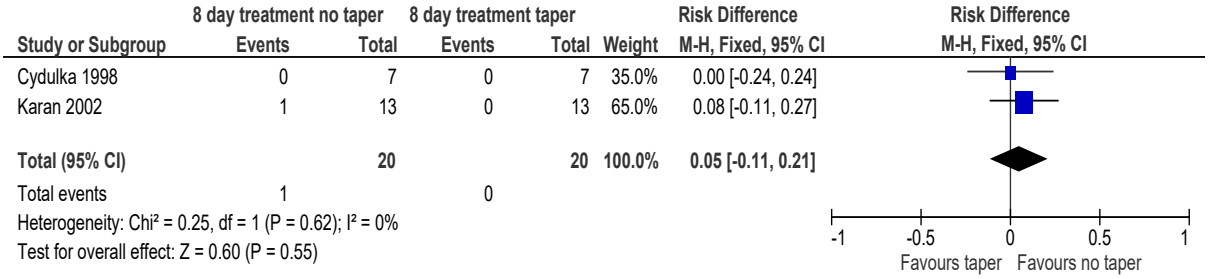


Figure 11: Adverse events - Fatigue at 6 months (lower is better)



E.4 8-day treatment with no taper vs. taper in acute asthma

Figure 12: Incidence of adrenal insufficiency- HPA axis suppression at 12 days (lower is better)



Appendix F GRADE tables

Table 11: Clinical evidence profile: rapid tapering versus slow tapering in Myasthenia gravis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Myasthenia gravis - Rapid-tapering prednisone**	**Slow-tapering prednisone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment successful attainment of minimal manifestation status without prednisone treatment at 12 months and without relapse or prednisone resumption at 15 months (follow-up: 12 months) (higher is better)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	23/59 (39.0%)	5/58 (8.6%)	**RR 4.52** (1.84 to 11.09)	**303 more per 1,000** (from 72 more to 870 more)	⊕⊕⊕◯ Moderate	CRITICAL
Adverse events - Nausea at 15 months (follow-up: 15 months) (lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	7/59 (11.9%)	7/58 (12.1%)	**RR 0.98** (0.37 to 2.63)	**2 fewer per 1,000** (from 76 fewer to 197 more)	⊕◯◯◯ Very low	CRITICAL
Adverse event - Diarrhoea at 15 months (follow-up: 15 months) (lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Myasthenia gravis - Rapid-tapering prednisone	Slow-tapering prednisone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/59 (5.1%)	1/58 (1.7%)	**RR 2.95** (0.32 to 27.54)	**34 more per 1,000** (from 12 fewer to 458 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events - Hyperkalemia at 15 months (lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	12/59 (20.3%)	16/58 (27.6%)	**RR 0.74** (0.38 to 1.42)	**72 fewer per 1,000** (from 171 fewer to 116 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events - Hyponatremia at 15 months (lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/59 (1.7%)	0/58 (0%)	**OR 7.26** (0.14 to 366)	**20 more per 1,000** (from 30 fewer to 60 more)[c]	⊕◯◯◯ Very low	CRITICAL

- CI: confidence interval; RR: risk ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to missing outcome data)
b. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8, 1.25)

c. Calculated with RD due to 0 events in one arm of a single study.

Table 12: Clinical evidence profile: short taper versus long taper in steroid sensitive nephrotic syndrome

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroid sensitive nephrotic syndrome - short taper**	**long taper**	**Relative (95% CI)**	**Absolute (95% CI)**		
Successful cessation of steroids - Maintenance low dose PDN treatment required at 6 months (follow-up: 6 months) (lower is better)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	13/38 (34.2%)	14/40 (35.0%)	**RR 0.98** (0.53 to 1.80)	**7 fewer per 1,000** (from 164 fewer to 280 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events - Adrenal suppression specific at 6 months (follow-up: 6 months) (lower is better)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	0/38 (0.0%)	0/40 (0.0%)	**RD 0.00** (-0.05 to 0.05)	**0 fewer per 1,000** (from 50 fewer to 50 more)	⊕⊕⊕◯ Moderate	CRITICAL

- **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8-1.25)
b. Downgraded by 1 increment for imprecision due to zero events and small sample size.

Table 13: Clinical evidence profile: taper after intravenous methylprednisolone compared to no taper in multiple sclerosis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MS - taper after IV MP	no taper	Relative (95% CI)	Absolute (95% CI)		
Incidence of adrenal insufficiency - as reported by study at 6 months (follow-up: 6 months) (lower is better)												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	0/45 (0.0%)	0/46 (0.0%)	**RD 0.00** (-0.06 to 0.06)	**0 fewer per 1,000** (from 60 fewer to 60 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events - Nausea at 6 months (follow-up: 6 months) (lower is better)												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d]	none	1/45 (2.2%)	2/46 (4.3%)	**RR 0.60** (0.08 to 4.26)	**17 fewer per 1,000** (from 40 fewer to 142 more)	⊕◯◯◯ Very low	CRITICAL
Adverse events - Fatigue at 6 months (follow-up: 6 months) (lower is better)												
2	randomised trials	serious[a]	not serious	serious[b]	very serious[d]	none	1/45 (2.2%)	3/46 (6.5%)	**RR 0.42** (0.07 to 2.67)	**38 fewer per 1,000** (from 61 fewer to 109 more)	⊕◯◯◯ Very low	CRITICAL

- **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by 1 increment as the majority of the evidence was of high risk of bias (due to missing outcome data)
b. Downgraded by 1 increment for population indirectness: The study excluded participants using any corticosteroids in the last thirty days before entering the study.
c. Downgraded by 1 increment for imprecision due to zero events and small sample size.

d. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8-1.25)

Table 14: Clinical evidence profile: 8-day treatment with no taper vs. taper in acute asthma

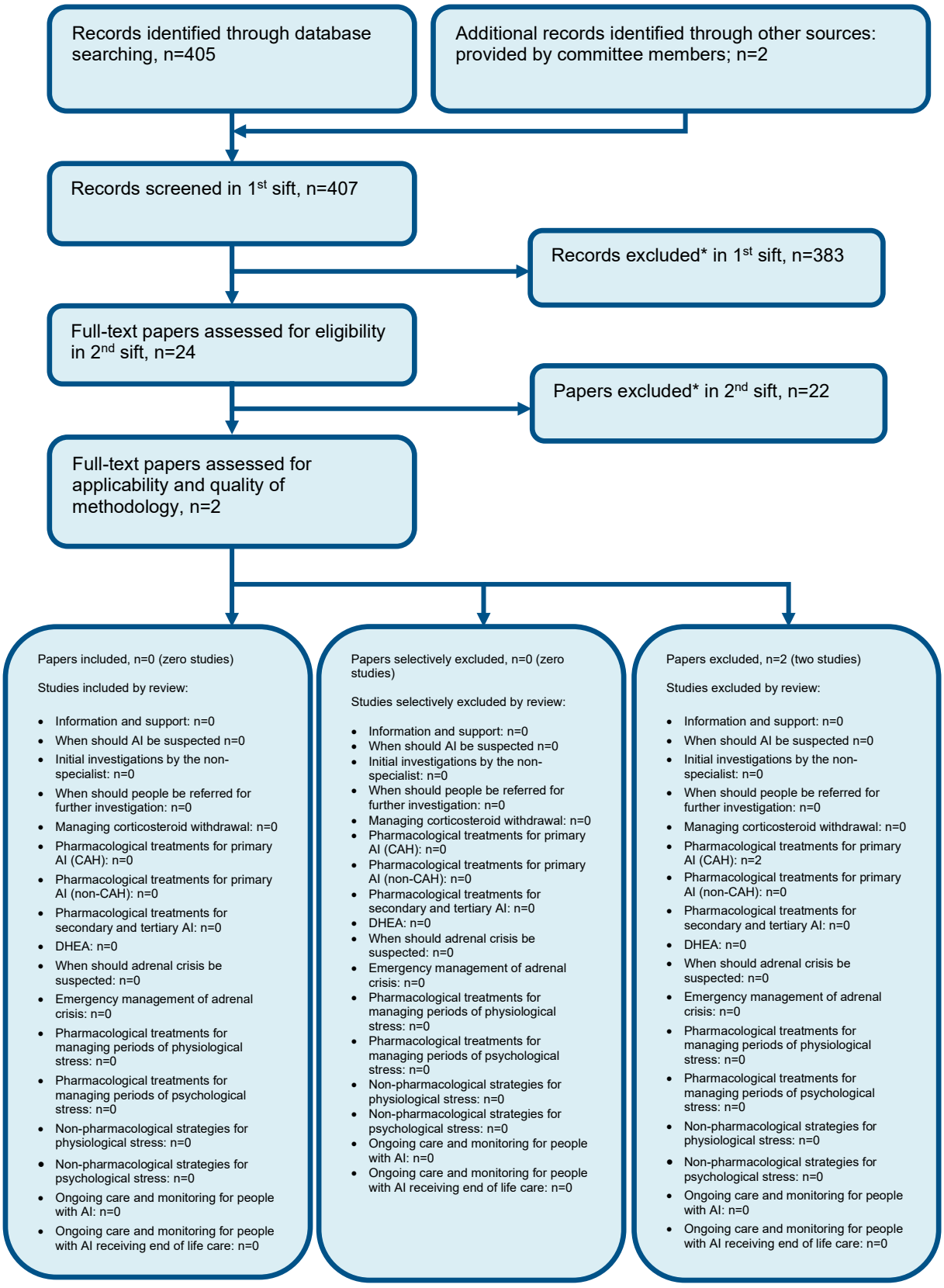
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acute asthma - 8 day treatment no taper**	**taper**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incidence of adrenal insufficiency- HPA axis suppression at 12 days (follow-up: 12 days) (lower is better)												
2	randomised trials	very serious[a]	serious[b]	serious[c]	serious[d]	none	1/20 (5.0%)	1/20 (5.0%)	**RD 0.05** (-0.11 to 0.21)	**50 fewer per 1,000** (from 110 fewer to 210 more)	⊕◯◯◯ Very low	CRITICAL

- **CI:** confidence interval

Explanations

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to a mixture of bias arising from the randomisation process and bias due to deviations from the intended interventions)
b. Downgraded by 1 increment for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
c. Downgraded by 1 increment for population indirectness: The study excluded patients already using oral steroids, and those requiring chronic steroid use, as defined by daily steroid use. To eliminate subjects in whom adrenal suppression might be present secondary to long-term steroid use.
d. Downgraded by 1 increment for imprecision due to zero events and small sample size.

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 14: Studies excluded from the clinical review

Study	Reason for exclusion
(2000) A randomisedcontrolled comparison of five days versus ten days of oral steroid therapy inacute adult asthma. Thorax 55(Suppl 3): A30	- Conference abstract
Aaron, S D; Dales, R E; Pham, B (1998) Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials. Respiratory medicine 92(8): 1059-65	- Systematic review used as source of primary studies
Abe, Yoshiyuki, Fujibayashi, Kazutoshi, Nishizaki, Yuji et al. (2020) Conventional versus Rapid Glucocorticoid Tapering in Severe Systemic Lupus Erythematosus Patients: A Non-Blind, Randomized Controlled Trial. Acta medica Okayama 74(2): 179-183	- Study design not relevant to this review protocol *Protocol only*
Ahsan, N, Hricik, D, Matas, A et al. (1999) Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil--a prospective randomized study. Steroid Withdrawal Study Group. Transplantation 68(12): 1865-74	- Comparator in study does not match that specified in this review protocol
Akashi, Kenichi, Mezawa, Hidetoshi, Tabata, Yuichi et al. (2016) Optimal step-down approach for pediatric asthma controlled by salmeterol/fluticasone: A randomized, controlled trial (OSCAR study). Allergology international : official journal of the Japanese Society of Allergology 65(3): 306-11	- Study does not contain an intervention relevant to this review protocol
Akdemir, Gulsah, Verheul, Marije K, Heimans, Lotte et al. (2016) Predictive factors of radiological progression after 2 years of remission-steered treatment in early arthritis patients: a post hoc analysis of the IMPROVED study. RMD open 2(1): e000172	- Study does not contain an intervention relevant to this review protocol
Alves, Cresio; Robazzi, Teresa Cristina Vicente; Mendonca, Milena (2008) Withdrawal from glucocorticosteroid therapy: clinical practice recommendations. Jornal de pediatria 84(3): 192-202	- Review article but not a systematic review
Anonymous. (1995) Withdrawal of corticosteroid therapy after acute asthma attacks. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 153(10): 1471-1473	- Review article but not a systematic review

Study	Reason for exclusion
Aref, Ahmed; Sharma, Ajay; Halawa, Ahmed (2021) Does steroid-free immunosuppression improve the outcome in kidney transplant recipients compared to conventional protocols?. World journal of transplantation 11(4): 99-113	- Systematic review used as source of primary studies
Armstrong, D L, Penrice, J, Bloomfield, F H et al. (2002) Follow up of a randomised trial of two different courses of dexamethasone for preterm babies at risk of chronic lung disease. Archives of disease in childhood. Fetal and neonatal edition 86(2): f102-7	- Study does not contain an intervention relevant to this review protocol
Assy, Nimer, Adams, Paul C, Myers, Paul et al. (2007) Randomized controlled trial of total immunosuppression withdrawal in liver transplant recipients: role of ursodeoxycholic acid. Transplantation 83(12): 1571-6	- Study does not contain an intervention relevant to this review protocol
Bacon, P A, Myles, A B, Beardwell, C G et al. (1966) Corticosteroid withdrawal in rheumatoid arthritis. Lancet (London, England) 2(7470): 935-7	- Study design not relevant to this review protocol
Balfour-Lynn, Ian M, Lees, Belinda, Hall, Pippa et al. (2006) Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. American journal of respiratory and critical care medicine 173(12): 1356-62	- Comparator in study does not match that specified in this review protocol
Bansal SB Sethi, S Sharma R Jain M Jha P Ahlawat R Duggal RKher V (2014) Early corticosteroid withdrawal regimen in a living donor kidney transplantation program. Indian journal of nephrology 24(4): 232-238	- Study design not relevant to this review protocol *retrospective study design*
Bel EH, Wenzel SE, Thompson PJ et al. (2014) Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. The New England journal of medicine 371(13): 1189-1197	- Incorrect comparator
Bergstra, Sytske Anne, Olivas, Otto, Akdemir, Gulsah et al. (2017) Further Treatment Intensification in Undifferentiated and Rheumatoid Arthritis Patients Already in Low Disease Activity has Limited Benefit towards Physical Functioning. Arthritis research & therapy 19(1): 220	- Study design not relevant to this review protocol
Beris, P, Burger, A, Favre, L et al. (1986) Adrenocortical responsiveness after discontinuous corticosteroid therapy. Klinische Wochenschrift 64(2): 70-5	- Study does not contain an intervention relevant to this review protocol
Boers M, Verhoeven AC, Markusse HM et al. (1997) Randomised comparison of combined step-down prednisolone, methotrexate and	- No useable outcome data reported

Study	Reason for exclusion
sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet (London, England) 350(9074): 309-318	
Boers, Maarten, van Tuyl, Lilian, van den Broek, Marianne et al. (2013) Meta-analysis suggests that intensive non-biological combination therapy with step-down prednisolone (COBRA strategy) may also 'disconnect' disease activity and damage in rheumatoid arthritis. Annals of the rheumatic diseases 72(3): 406-9	- No useable outcome data reported
Boletis, J N, Konstadinidou, I, Chelioti, H et al. (2001) Successful withdrawal of steroid after renal transplantation. Transplantation proceedings 33(12): 1231-3	- Comparator in study does not match that specified in this review protocol
Boletis, JN, Konstadinidou, I, Chelioti, H et al. (2000) Successful withdrawal of steroids after renal transplantation. XVIII international congress of the transplantation society; 2000 aug 27-sept 1; rome, italy	- Conference abstract
Boots, JM, Christiaans, MH, van Duijnhoven, EM et al. (2002) Early steroid withdrawal in renal transplantation with tacrolimus dual therapy: a pilot study. Transplantation proceedings 34(5): 1698-1699	- No useable outcome data reported
Boots, JMM, Christaiaans, MHL, van Duijnhoven, EM et al. (2002) Early steroid withdrawal in renal transplant recipients with tacrolimus dual therapy. Xixth international congress of the transplantation society; 2002 aug 25-30; miami, FL	- Full text paper not available
Boots, Johannes M M, Christiaans, M H I, van Duijnhoven, E M et al. (2002) Early steroid withdrawal in renal transplantation with tacrolimus dual therapy: a pilot study. Transplantation proceedings 34(5): 1698-9	- Secondary publication of an included study that does not provide any additional relevant information
Boots, Johannes M M, Christiaans, Maarten H L, Van Duijnhoven, Elly M et al. (2002) Early steroid withdrawal in renal transplantation with tacrolimus dual therapy: a pilot study. Transplantation 74(12): 1703-9	- No useable outcome data reported
Brignola, C, De Simone, G, Belloli, C et al. (1994) Steroid treatment in active Crohn's disease: a comparison between two regimens of different duration. Alimentary pharmacology & therapeutics 8(4): 465-8	- No useable outcome data
Brignola, C, De Simone, G, Iannone, P et al. (1992) Influence of steroid treatment's duration	- No useable outcome data

Study	Reason for exclusion
in patients with active Crohn's disease. Agents and actions specno: c90-2	
Broersen, L.H.A., Pereira, A.M., Jorgensen, J.O.L. et al. (2015) Adrenal insufficiency in corticosteroids use: Systematic review and metaanalysis. Nederlands Tijdschrift voor Geneeskunde 159(38)	- Duplicate reference
Broersen, Leonie H A, Pereira, Alberto M, Jorgensen, Jens Otto L et al. (2015) Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 100(6): 2171-80	- Systematic review used as source of primary studies
Bruce, Ian N, Furie, Richard A, Morand, Eric F et al. (2022) Concordance and discordance in SLE clinical trial outcome measures: analysis of three anifrolumab phase 2/3 trials. Annals of the rheumatic diseases 81(7): 962-969	- Study does not contain an intervention relevant to this review protocol
Bruce, Ian N, van Vollenhoven, Ronald F, Morand, Eric F et al. (2022) Sustained glucocorticoid tapering in the phase 3 trials of anifrolumab: a post-hoc analysis of the TULIP-1 and TULIP-2 trials. Rheumatology (Oxford, England)	- Comparator in study does not match that specified in this review protocol
Budde, K, Diekmann, F, Fritsche, L et al. (2001) Steroid withdrawal in long-term cyclosporine treated patients using mycophenolate mofetil: a prospective randomized pilot study. A transplant odyssey; 2001 aug 20-23; istanbul, turkey	- Conference abstract
Budde, K, Fritsche, L, Geissler, S et al. (2001) Steroid withdrawal in long-term cyclosporine A treated patients using mycophenolate mofetil: a prospective randomized pilot study. Transplantation proceedings 33(78): 3250-2	- Comparator in study does not match that specified in this review protocol
Budde, K, Geissler, S, Hallebach, G et al. (2002) Prospective randomized pilot study of steroid withdrawal with mycophenolate mofetil in long-term cyclosporine-treated patients: 4-year follow-up. Transplantation proceedings 34(5): 1703-5	- Comparator in study does not match that specified in this review protocol
Bultman, E; Kuipers, E J; van der Woude, C J (2010) Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics 32(3): 313-23	- Systematic review used as source of primary studies
Burlingham, W J; Grailer, A; Sollinger, H W (1989) Changes in donor-specific cell-mediated lympholysis (CML) response associated with	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
success of early steroid withdrawal in DST-azathioprine-treated renal transplant recipients. Transplantation proceedings 21(1pt2): 1818-9	
Buttgereit, F., Nebesky, J.M., Burmester, G. et al. (2019) Glucocorticoid tapering in monthly 1-mg decrements does not result in clinically manifest adrenal insufficiency in patients with rheumatoid arthritis: Learnings from a phase 3/4 study. Arthritis and Rheumatology 71(supplement10): 2409-2410	- Conference abstract
Buttgereit, F., Nebesky, J.M., Burmester, G.R. et al. (2019) Glucocorticoid tapering in monthly 1-mg decrements does not result in clinically manifest adrenal insufficiency in patients with rheumatoid arthritis: Learnings from the phase 3/4 semira study. Annals of the Rheumatic Diseases 78(supplement2): 336	- Conference abstract
Campbell, Ashley M; Martin, Jennifer R; Erstad, Brian L (2020) Corticosteroid Tapering Regimens in Rheumatic Disease: A Systematic Review. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 26(2): 41-47	- Systematic review used as source of primary studies
Chang AB, Clark R, Sloots TP et al. (2008) A 5- versus 3-day course of oral corticosteroids for children with asthma exacerbations who are not hospitalised: a randomised controlled trial. The Medical journal of Australia 189(6): 306-310	- Study does not contain an intervention relevant to this review protocol
Chapman, K.R., Hurst, J., Frent, S. et al. (2018) Withdrawal of inhaled corticosteroids from COPD patients inhaling long-term triple therapy: The sunset study. American Journal of Respiratory and Critical Care Medicine 197(meetingabstracts)	- Comparator in study does not match that specified in this review protocol
Chen, Z-S, He, F, Zeng, F-J et al. (2007) Early steroid withdrawal after liver transplantation for hepatocellular carcinoma. World journal of gastroenterology 13(39): 5273-5276	- Comparator in study does not match that specified in this review protocol
Choudhury, Aklak B, Dawson, Carolyn M, Kilvington, Hazel E et al. (2007) Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respiratory research 8: 93	- Study does not contain an intervention relevant to this review protocol
Citterio, A, La Mantia, L, Ciucci, G et al. (2000) Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies

Study	Reason for exclusion
Citterio, F, Baldan, N, Tondolo, E et al. (2004) Medium term results of steroid withdrawal in tacrolimus treated renal transplant recipients. 3rd international congress on immunosuppression; 2004 dec 8-11; san diego (CA)	- Conference abstract
Citterio, F, Rigotti, P, Scata, M C et al. (2002) Steroid withdrawal from tacrolimus-based therapy in renal transplant patients. Transplantation proceedings 34(5): 1707-8	- Comparator in study does not match that specified in this review protocol
Citterio, F, Sparacino, V, Altieri, P et al. (2005) Addition of sirolimus to cyclosporine in long-term kidney transplant recipients to withdraw steroid. Transplantation proceedings 37(2): 827-9	- No useable outcome data reported
Collinson, Neil, Tuckwell, Katie, Habeck, Frank et al. (2015) Development and implementation of a double-blind corticosteroid-tapering regimen for a clinical trial. International journal of rheumatology 2015: 589841	- Study design not relevant to this review protocol *protocol only*
Coppelli, A, Buonomo, O, Iaria, G et al. (2001) Preliminary results of a prospective randomized study of basiliximab and steroid withdrawal in kidney transplantation. A transplant odyssey; 2001 aug 20-23; istanbul, turkey	- Conference abstract
Cristinelli, L, Brunori, G, Manganoni, AM et al. (1986) Controlled study of steroid withdrawal after 6 months in renal transplant patients treated with ciclosporin. Contributions to nephrology 51: 91-95	- Comparator in study does not match that specified in this review protocol
Cristinelli, L, Brunori, G, Setti, G et al. (1987) Withdrawal of methylprednisolone at the sixth month in renal transplant recipients treated with cyclosporine. Transplantation proceedings 19(1pt3): 2021-3	- Comparator in study does not match that specified in this review protocol
Cristinelli, L, Brunori, G, Setti, G et al. (1986) Controlled randomised trial of methylprednisolone withdrawal at the sixth month in renal transplant recipients treated with cyclosporin. Nephrology dialysis transplantation 1(2): 139	- Conference abstract
CriÃ©e, C P, Oster, H, Richter, A et al. (2002) Tapering of systemic corticosteroids using HFA beclomethasone in adults with severe asthma. American journal of respiratory and critical care medicine 165(suppl8): a768	- Conference abstract
Cummins, C (2003) Long term tapering versus standard Prednisolone therapy for the treatment of the initial episode of childhood nephrotic	- Full text paper not available

Study	Reason for exclusion
syndrome: national multi-centre randomised double blind pilot study. National research register, UK [http://www.nrr.nhs.uk/]	
De Carlis, L, Belli, L S, Rondinara, G F et al. (1997) Early steroid withdrawal in liver transplant patients: final report of a prospective randomized trial. Transplantation proceedings 29(12): 539-42	- Comparator in study does not match that specified in this review protocol
Delgado, D, Arazi, H C, Sellanes, M et al. (1999) Study of early corticosteroid withdrawal in cardiac transplantation. Transplantation proceedings 31(6): 2524-5	- Study design not relevant to this review protocol
DeMartini, TJ and Muraskas, JK (1999) Pulse versus tapered dosing dexamethasone for evolving bronchopulmonary dysplasia (BPD). Pediatric research 45(4): 300a	- Conference abstract
Dernis, Emmanuelle, Ruyssen-Witrand, Adeline, Mouterde, Gael et al. (2010) Use of glucocorticoids in rheumatoid arthritis - pratical modalities of glucocorticoid therapy: recommendations for clinical practice based on data from the literature and expert opinion. Joint bone spine 77(5): 451-7	- Review article but not a systematic review
Dudley, CR and Ratcliffe, PJ (1994) Effect of steroid withdrawal on graft function in renal transplant recipients. Nephrology dialysis transplantation 9(11): 1672	- Conference abstract
Dunn, T, Asolati, M, Holman, D et al. (1998) Long-term outcome of kidney transplantation after steroid withdrawal. Transplantation proceedings 30(5): 1788-9	- Study design not relevant to this review protocol
Elnoby, A.S. and Nassar, H.S. (2021) Corticosteroid-associated hypothalamic-pituitary-adrenal axis suppression in brain tumours: a focus on dosing and tapering. Journal of Pharmacy Practice and Research 51(4): 300-306	- Systematic review used as source of primary studies
Everson, G T, Trouillot, T, Wachs, M et al. (1999) Early steroid withdrawal in liver transplantation is safe and beneficial. Liver transplantation and surgery : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 5(4suppl1): 48-57	- Review article but not a systematic review
Farrero, E, Llunell, A, Canete, C et al. (1995) Inhaled steroids treatment and withdrawal in asthmatic children. Allergologia et immunopathologia 23(4): 182-8	- Study design not relevant to this review protocol

Study	Reason for exclusion
Frei, D, Keusch, G, Hugentobler, M et al. (1989) Withdrawal of steroids after cadaveric kidney allotransplantation on maintenance triple therapy. Transplantation proceedings 21(1pt2): 1620-2	- Study design not relevant to this review protocol
Fu, Lisheng, Xiang, Rong, Zhang, Wei et al. (2022) The comparation of different oral corticosteroids withdrawal methods for nasal polyp surgery. Ear, nose, & throat journal: 1455613221086027	- Population not relevant to this review protocol *only taking steroids for 10 days*
Gerard, Anne-Laure, Simon-Tillaux, Noemie, Yordanov, Youri et al. (2021) Efficacy and safety of steroid-sparing treatments in giant cell arteritis according to the glucocorticoids tapering regimen: A systematic review and meta-analysis. European journal of internal medicine 88: 96-103	- Systematic review used as source of primary studies
Ghafouri, N, Sharieff, GQ, Rajasingham, A et al. (2010) Comparison of one-dose and two-dose regimes of oral dexamethasone in the management of acute asthma exacerbations in the pediatric emergency department. Pediatric emergency care 26(9): 705-706	- Study does not contain an intervention relevant to this review protocol
Giancane, Gabriella, Lavarello, Claudio, Pistorio, Angela et al. (2019) The PRINTO evidence-based proposal for glucocorticoids tapering/discontinuation in new onset juvenile dermatomyositis patients. Pediatric rheumatology online journal 17(1): 24	- No useable outcome data reported
Gibson, P G; Powell, H; Ducharme, F (2005) Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. The Cochrane database of systematic reviews: cd005076	- Systematic review used as source of primary studies
Giessing, Markus, Fuller, Tom Florian, Tuellmann, Max et al. (2007) Steroid- and calcineurin inhibitor free immunosuppression in kidney transplantation: state of the art and future developments. World journal of urology 25(3): 325-32	- Systematic review used as source of primary studies
Grenda, R.; Watson, A.; Tompeter., R.S. (2009) Early steroid withdrawal in paediatric kidney recipients after two-doses of Daclizumab induction, tacrolimus and MMF versus tacrolimus, MMF and steroids - the twist study. Pediatric Transplantation 13(suppl1): 154-155	- conference abstract
Grenda, R, Watson, A, Trompeter, R et al. (2010) A randomized trial to assess the impact	- incorrect comparator

Study	Reason for exclusion
of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 10(4): 828-836	
Gruessner, R W, Sutherland, D E, Parr, E et al. (2001) A prospective, randomized, open-label study of steroid withdrawal in pancreas transplantation-a preliminary report with 6-month follow-up. Transplantation proceedings 33(12): 1663-4	- Comparator in study does not match that specified in this review protocol
Gulati, S, Ahmed, M, Sharma, RK et al. (2003) Comparison of abrupt withdrawal versus slow tapering regimen of prednisolone therapy in the management of first episode of steroid responsive childhood idiopathic nephrotic syndrome. XXXVIII congress of the european renal association european dialysis and transplant association june 24-27 2001, vienna, austria: 132	- Conference abstract
Gulati, S, Ahmed, M, Sharma, RK et al. (2001) Comparison of abrupt withdrawal versus slow tapering regimen of prednisolone therapy in the management of first episode of steroid responsive childhood idiopathic nephrotic syndrome. Nephrology dialysis transplantation 16(6): a87	- Conference abstract
Gurnell, M, Heaney, L G, Price, D et al. (2021) Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. Journal of internal medicine 290(2): 240-256	- Systematic review used as source of primary studies
Hajar, Tamar, Leshem, Yael A, Hanifin, Jon M et al. (2015) A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. Journal of the American Academy of Dermatology 72(3): 541-549e2	- Systematic review used as source of primary studies
Hasegawa T, Ishihara K, Takakura S et al. (2000) Duration of systemic corticosteroids in the treatment of asthma exacerbation; a randomized study. Internal medicine (Tokyo, Japan) 39(10): 794-797	- Study does not contain an intervention relevant to this review protocol
Hatton MQ, Vathenen AS, Allen MJ et al. (1995) A comparison of 'abruptly stopping' with 'tailing off' oral corticosteroids in acute asthma. Respiratory medicine 89(2): 101-104	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Hebert, V., Vermeulin, T., Tanguy, L. et al. (2019) Comparison of real costs in the French healthcare system in newly diagnosed pemphigus patients: first-line treatment with rituximab versus standard corticosteroid regimen. Data of a national multicentre trial. The British journal of dermatology	- No useable outcome data reported
Hebert, V, Vermeulin, T, Tanguy, L et al. (2020) Comparison of real costs in the French healthcare system in newly diagnosed patients with pemphigus for first-line treatment with rituximab vs. standard corticosteroid regimen: data from a national multicentre trial. The British journal of dermatology 183(1): 121-127	- No useable outcome data reported
Hings, I M, Filipovich, A H, Miller, W J et al. (1993) Prednisone therapy for acute graft-versus-host disease: short- versus long-term treatment. A prospective randomized trial. Transplantation 56(3): 577-80	- No useable outcome data reported
Hoes, J N, Jacobs, J W G, Boers, M et al. (2007) EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases 66(12): 1560-7	- Review article but not a systematic review
Hollander, AA and Hene, RJ (1996) Late prednisone withdrawal in renal transplant patients. Nephrology dialysis transplantation 11(6): a276	- Full text paper not available
Hu, An Bin, Wu, Lin Wei, Tai, Qiang et al. (2013) Safety and efficacy of four steroid-minimization protocols in liver transplant recipients: 3-year follow-up in a single center. Journal of digestive diseases 14(1): 38-44	- Study design not relevant to this review protocol
Hu, An-bin, He, Xiao-shun, Wu, Zhi-peng et al. (2008) [Evaluation of efficacy and safety on steroid withdraw at the seventh day after liver transplantation]. Zhonghua wai ke za zhi [Chinese journal of surgery] 46(15): 1126-8	- Study not reported in English
Hwang, Jonwei and Lio, Peter A (2022) Topical corticosteroid withdrawal ('steroid addiction'): an update of a systematic review. The Journal of dermatological treatment 33(3): 1293-1298	- Systematic review used as source of primary studies
Jie, W.; Xiong, J.; Yan, X. (2021) Meta-analysis of prednisone in withdrawal therapy following medication overuse headache. Neurology Asia 26(4): 761-766	- Systematic review used as source of primary studies

Study	Reason for exclusion
Johansson, Mats W, Barthel, Steven R, Swenson, Cheri A et al. (2006) Eosinophil beta 1 integrin activation state correlates with asthma activity in a blind study of inhaled corticosteroid withdrawal. The Journal of allergy and clinical immunology 117(6): 1502-4	- Study design not relevant to this review protocol
Joseph, Rebecca M, Hunter, Ann Louise, Ray, David W et al. (2016) Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Seminars in arthritis and rheumatism 46(1): 133-41	- Systematic review used as source of primary studies
Juhasz, M.L.W., Curley, R.A., Rasmussen, A. et al. (2017) Systematic Review of the Topical Steroid Addiction and Topical Steroid Withdrawal Phenomenon in Children Diagnosed with Atopic Dermatitis and Treated with Topical Corticosteroids. Journal of the Dermatology Nurses' Association 9(5): 233-240	- Systematic review used as source of primary studies
Kayani S and Shannon DC (2002) Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. Chest 122(2): 624-628	- Study does not contain an intervention relevant to this review protocol
Keir, H.R., Richardson, H., Veluchamy, A. et al. (2022) The Effect of Inhaled Corticosteroid Withdrawal on Inflammation and the Airway Microbiome in COPD: The INCOGNITO Trial. American Journal of Respiratory and Critical Care Medicine 205(1)	- Conference abstract
Kim, B, Huh, W, Baek, HJ et al. (2003) Randomized trial of tacrolimus versus cyclosporine in steroid withdrawal in living donor renal transplant recipients. Journal of the American Society of Nephrology : JASN 14(nov): 648a	- No useable outcome data reported
Korn, Stephanie, Howarth, Peter, Smith, Steven G et al. (2022) Development of methodology for assessing steroid-tapering in clinical trials for biologics in asthma. Respiratory research 23(1): 45	- Systematic review used as source of primary studies
Kos-Kudla, B., Ciesielska-Kopacz, N., Ostrowska, Z. et al. (2003) Adrenal cortex function in asthmatic patients following the discontinuation of chronic therapy with systemic glucocorticosteroids. Journal of Clinical Pharmacy and Therapeutics 28(2): 103-108	- Study design not relevant to this review protocol
Kowalski, Marek L, Wojciechowski, Piotr, Dziewonska, Marta et al. (2016) Adrenal suppression by inhaled corticosteroids in	- Systematic review used as source of primary studies

Study	Reason for exclusion
patients with asthma: A systematic review and quantitative analysis. Allergy and asthma proceedings 37(1): 9-17	
Kramer, B.K., Klinger, M., Wlodarczyk, Z. et al. (2010) Tacrolimus combined with two different corticosteroid-free regimens compared with a standard triple regimen in renal transplantation: One year observational results. Clinical Transplantation 24(1): e1-e9	- Study design not relevant to this review protocol
Krause, Dietmar, Mai, Anna, Klaassen-Mielke, Renate et al. (2022) The Efficacy of Short-Term Bridging Strategies With High- and Low-Dose Prednisolone on Radiographic and Clinical Outcomes in Active Early Rheumatoid Arthritis: A Double-Blind, Randomized, Placebo-Controlled Trial. Arthritis & rheumatology (Hoboken, N.J.) 74(10): 1628-1637	- Study does not contain an intervention relevant to this review protocol
Ksiazek, J and Wyszynska, T (1995) Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. Acta paediatrica (Oslo, Norway : 1992) 84(8): 889-93	- No useable outcome data reported
Kumar, Mysore S Anil, Xiao, Sheng-Guang, Fyfe, Billie et al. (2005) Steroid avoidance in renal transplantation using basiliximab induction, cyclosporine-based immunosuppression and protocol biopsies. Clinical transplantation 19(1): 61-9	- Comparator in study does not match that specified in this review protocol
Kupin, W, Venkat, K K, Goggins, M et al. (1999) Improved outcome of steroid withdrawal in mycophenolate mofetil-treated primary cadaveric renal transplant recipients. Transplantation proceedings 31(12): 1131-2	- Study design not relevant to this review protocol
Kuypers, D R J, Evenepoel, P, Maes, B et al. (2003) The use of an anti-CD25 monoclonal antibody and mycophenolate mofetil enables the use of a low-dose tacrolimus and early withdrawal of steroids in renal transplant recipients. Clinical transplantation 17(3): 234-41	- Study does not contain an intervention relevant to this review protocol
Laftavi, Mark R, Stephan, Rabie, Stefanick, Barbara et al. (2005) Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. Surgery 137(3): 364-71	- Comparator in study does not match that specified in this review protocol
Landi, B., Anh, T.N., Cortot, A. et al. (1992) Endoscopic monitoring of Crohn's disease treatment: A prospective, randomized clinical trial. Gastroenterology 102(5): 1647-1653	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Langton Hewer S, Hobbs J, Reid F et al. (1998) Prednisolone in acute childhood asthma: clinical responses to three dosages. Respiratory medicine 92(3): 541-546	- Study does not contain an intervention relevant to this review protocol
Lapperre, T.S., Janner, J., Laub, R.R. et al. (2019) Eosinophil-guided corticosteroid-sparing therapy in hospitalized patients with exacerbated COPD(CORTICOsteroid Reduction in COPD (CORTICO-COP)): A randomized prospective multicenter investigator-initiated trial. American Journal of Respiratory and Critical Care Medicine 199(9)	- Study does not contain an intervention relevant to this review protocol
Laugesen, Kristina, Broersen, Leonie H A, Hansen, Simon Boggild et al. (2021) MANAGEMENT OF ENDOCRINE DISEASE: Glucocorticoid-induced adrenal insufficiency: replace while we wait for evidence?. European journal of endocrinology 184(4): r111-r122	- Review article but not a systematic review
Lebranchu, Y, Aubert, P, Bayle, F et al. (2000) Could steroids be withdrawn in renal transplant patients sequentially treated with ATG, cyclosporine, and cellcept? One-year results of a double-blind, randomized, multicenter study comparing normal dose versus low-dose and withdrawal of steroids. M 55002 French Study Group. Transplantation proceedings 32(2): 396-7	- Comparator in study does not match that specified in this review protocol
Lederle, F A, Pluhar, R E, Joseph, A M et al. (1987) Tapering of corticosteroid therapy following exacerbation of asthma. A randomized, double-blind, placebo-controlled trial. Archives of internal medicine 147(12): 2201-3	- No useable outcome data
Li, Huiping, He, Guojun, Chu, Haiqing et al. (2003) A step-wise application of methylprednisolone versus dexamethasone in the treatment of acute exacerbations of COPD. Respirology (Carlton, Vic.) 8(2): 199-204	- Study does not contain an intervention relevant to this review protocol
Lian, D. (2014) An efficiency and safety of short-term prednisone treating to moderate and severe subacute thyroiditis. Endocrine Reviews 35(suppl3)	- Conference abstract
Liaw, YF, Sheen, IS, Lin, SM et al. (1991) Prednisolone withdrawel followed by recombinant alfa-interferon in chronic non-A, non-B hepatitis. Gastroenterologia Japonica 26suppl: 3247-3250	- Conference abstract
Ligtenberg, Jack J M and Zijlstra, Jan G (2004) The relative adrenal insufficiency syndrome	- Review article but not a systematic review

Study	Reason for exclusion
revisited: which patients will benefit from low-dose steroids?. Current opinion in critical care 10(6): 456-60	
Lin, Lu-Lu, Gu, Hui-Yun, Luo, Jie et al. (2019) Impact and Beneficial Critical Points of Clinical Outcome in Corticosteroid Management of Adult Patients With Sepsis: Meta-Analysis and GRADE Assessment. Frontiers in pharmacology 10: 1101	- Systematic review used as source of primary studies
Lipworth, Brian J, Short, Philip M, Williamson, Peter A et al. (2012) A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial. Chest 141(3): 607-615	- Study does not contain an intervention relevant to this review protocol
Lloveras, J, Puig, J M, Comerma, I et al. (1990) Requirements for safe prednisone discontinuation in late renal transplantation in recipients immunosuppressed with cyclosporine. Transplantation proceedings 22(4): 1693-4	- Study design not relevant to this review protocol
Maiorca, R, Cristinelli, L, Brunori, G et al. (1988) Prospective controlled trial of steroid withdrawal after six months in renal transplant patients treated with cyclosporine. Transplantation proceedings 20(3suppl3): 121-5	- Study design not relevant to this review protocol
Marr, Bonnie L, Mettelman, Barbara B, Bode, Michelle M et al. (2019) Randomized Trial of 42-Day Compared with 9-Day Courses of Dexamethasone for the Treatment of Evolving Bronchopulmonary Dysplasia in Extremely Preterm Infants. The Journal of pediatrics 211: 20-26e1	- Study does not contain an intervention relevant to this review protocol
Matas, A and Ewell, M (1999) Prednisone withdrawal in kidney transplant recipients on CSA/MMF - a prospective randomized study. Transplantation 67(9): 543	- Conference abstract
McDiarmid, S V, Farmer, D A, Goldstein, L I et al. (1995) A randomized prospective trial of steroid withdrawal after liver transplantation. Transplantation 60(12): 1443-50	- No useable outcome data reported
McHutchison, JG, Pockros, PJ, Bylund, D et al. (1994) Prednisone withdrawal followed by alpha interferon for chronic HCV infection: results of a randomized controlled trial. Hepatology (Baltimore, Md.) 20(4pt2): 156a	- Conference abstract
Meier-Kriesche, H-U; Magee, J C; Kaplan, B (2008) Trials and tribulations of steroid withdrawal after kidney transplantation. American journal of transplantation : official	- Review article but not a systematic review

Study	Reason for exclusion
journal of the American Society of Transplantation and the American Society of Transplant Surgeons 8(2): 265-6	
Menzies-Gow, A., Corren, J., Bel, E. et al. (2019) Oral corticosteroid tapering during benralizumab treatment of severe, uncontrolled eosinophilic asthma: PONENTE phase IIIb clinical trial. American Journal of Respiratory and Critical Care Medicine 199(9)	- Incorrect comparator
Menzies-Gow, Andrew, Corren, Jonathan, Bel, Elisabeth H et al. (2019) Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. ERJ open research 5(3)	- Incorrect comparator
Mericq, Veronica, Salas, Paulina, Pinto, Viola et al. (2013) Steroid withdrawal in pediatric kidney transplant allows better growth, lipids and body composition: a randomized controlled trial. Hormone research in paediatrics 79(2): 88-96	- Comparator in study does not match that specified in this review protocol
Midtvedt, Karsten, Hjelmesaeth, Joran, Hartmann, Anders et al. (2004) Insulin resistance after renal transplantation: the effect of steroid dose reduction and withdrawal. Journal of the American Society of Nephrology : JASN 15(12): 3233-9	- No useable outcome data reported
Minneci, Peter C, Deans, Katherine J, Banks, Steven M et al. (2004) Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Annals of internal medicine 141(1): 47-56	- Systematic review used as source of primary studies
Mizuno, Y, Kikuchi, H, Fujimori, K et al. (2000) Trial of steroid withdrawal in renal transplant recipients with long-term--surviving allograft. Transplantation proceedings 32(7): 1677-8	- Study design not relevant to this review protocol
Moench, C, Barreiros, A P, Schuchmann, M et al. (2007) Tacrolimus monotherapy without steroids after liver transplantation--a prospective randomized double-blinded placebo-controlled trial. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 7(6): 1616-23	- No useable outcome data
Mohan, S.; Han, J.; Stone, J.H. (2020) Efficacy of adjunctive methotrexate in patients with giant cell arteritis treated with tocilizumab plus prednisone tapering: subanalysis of the giacta trial. Annals of the Rheumatic Diseases 79(suppl1): 693	- Conference abstract

Study	Reason for exclusion
Montero, Nuria, Webster, Angela C, Royuela, Ana et al. (2014) Steroid avoidance or withdrawal for pancreas and pancreas with kidney transplant recipients. The Cochrane database of systematic reviews: cd007669	- Systematic review used as source of primary studies
Morris, P. and Knight, S. (2010) Steroid sparing protocols following non-renal transplantation: A systematic review and meta-analysis. Transplantation 90(suppl1): 641	- Conference abstract
Mourad, G., Glyda, M., Albano, L. et al. (2014) Incidence of new onset diabetes mellitus after de novo kidney transplantation (NODAT) with two tacrolimus prolonged release corticosteroid (CS) withdrawal regimens. Transplantation 98(suppl1): 116	- Conference abstract
Nadeem, Nighat J; Taylor, Stephanie J C; Eldridge, Sandra M (2011) Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. Respiratory research 12: 107	- Systematic review used as source of primary studies
Nair, A, Vaidyanathan, S, Clearie, K et al. (2010) Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis. Allergy 65(3): 359-67	- Study does not contain an intervention relevant to this review protocol
Nakache, Richard, Malaise, Jacques, Van Ophem, Dominique et al. (2005) A large, prospective, randomized, open-label, multicentre study of corticosteroid withdrawal in SPK transplantation: a 3-year report. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 20suppl2: ii40-ii62	- No useable outcome data reported
Neumann, T., Stone, J.H., Bao, M. et al. (2019) Long-term outcome of tocilizumab for patients with giant cell arteritis: Results from part 2 of the GiACTA trial. Swiss Medical Weekly 149(supplement238): 15s	- Conference abstract
Newstead, C and Moore, R (1989) Renal Transplant Function After Steroid Withdrawal from Triple Immunosuppression. Nephrology dialysis transplantation 4: 518	- Conference abstract
Niewoehner DE, Erbland ML, Deupree RH et al. (1999) Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. The New England journal of medicine 340(25): 1941-1947	- Study does not contain an intervention relevant to this review protocol *2 different treatment regimes not focused on withdrawal.*

Study	Reason for exclusion
Normansell, Rebecca; Kew, Kayleigh M; Mansour, George (2016) Different oral corticosteroid regimens for acute asthma. The Cochrane database of systematic reviews: cd011801	- Systematic review used as source of primary studies
Nowacka-Cieciura, E., Durlik, M., Cieciura, T. et al. (2002) Elevated serum immunoglobulins after steroid withdrawal in renal allograft recipients. Transplantation Proceedings 34(2): 564-566	- Comparator in study does not match that specified in this review protocol
Nowacka-Cieciura, E, Durlik, M, Cieciura, T et al. (2001) Positive effect of steroid withdrawal on bone mineral density in renal allograft recipients. Transplantation proceedings 33(12): 1273-7	- Comparator in study does not match that specified in this review protocol
Nowacka-Cieciura, Ewa, Durlik, M, Cieciura, T et al. (2002) Steroid withdrawal after renal transplantation--risks and benefits. Transplantation proceedings 34(2): 560-3	- Comparator in study does not match that specified in this review protocol
O'Driscoll BR, Kalra S, Wilson M et al. (1993) Double-blind trial of steroid tapering in acute asthma. Lancet (London, England) 341(8841): 324-327	- No useable outcome data reported
Ouzan, D, Guisset, M, Prignet, JM et al. (1994) French controlled trial of prednisolone withdrawal followed by interferon alpha 2b in chronic hepatitis C Does a pulse corticosteroid therapy increase the response at 6 and 12 months? (AASLD abstract). Hepatology (Baltimore, Md.) 20(4pt2): 383a	- Full text paper not available
Pageaux, GP, Boillot, O, Calmus, Y et al. (2003) Early steroid withdrawal after liver transplanation: a placebo controlled study. Hepatology (Baltimore, Md.) 38(4suppl1): 370a	- Conference abstract
Pagnoux, Christian, Quemeneur, Thomas, Ninet, Jacques et al. (2015) Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. Arthritis & rheumatology (Hoboken, N.J.) 67(4): 1117-27	- Study does not contain an intervention relevant to this review protocol
Pankewycz, OG, Stephan, R, Stefanick, B et al. (2004) The clinical benefits of early steroid withdrawal (7 days) and utility of protocol biopsies at 1, 6 and 12 months in guiding steroid-free immunosuppressive therapy after renal transplantation. American journal of transplantation 4(suppl8): 579	- Conference abstract

Study	Reason for exclusion
Park, Jae Berm, Kim, Sung-Joo, Oh, Ha Young et al. (2006) Steroid withdrawal in living donor renal transplant recipients using tacrolimus and cyclosporine: a randomized prospective study. Transplant international : official journal of the European Society for Organ Transplantation 19(6): 478-84	- No useable outcome data reported
Pascual, J., Galeano, C., Quereda, C. et al. (2009) Steroid avoidance or withdrawal for pancreas and kidney transplant recipients. Cochrane Database of Systematic Reviews: cd007669	- Systematic review used as source of primary studies
Pascual, Julio, Galeano, Cristina, Royuela, Ana et al. (2010) A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. Transplantation 90(4): 343-9	- Systematic review used as source of primary studies
Pascual, Julio, Quereda, Carlos, Zamora, Javier et al. (2004) Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. Transplantation 78(10): 1548-56	- Systematic review used as source of primary studies
Pascual, Julio, Royuela, Ana, Galeano, Cristina et al. (2012) Very early steroid withdrawal or complete avoidance for kidney transplant recipients: a systematic review. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 27(2): 825-32	- Systematic review used as source of primary studies
Pascual, Julio, Zamora, Javier, Galeano, Cristina et al. (2009) Steroid avoidance or withdrawal for kidney transplant recipients. The Cochrane database of systematic reviews: cd005632	- Systematic review used as source of primary studies
Perez, V, Findor, J, Tanno, H et al. (1990) Recombinant interferon alpha 2b (IFN) with and without prednisone withdrawal Comparative study. Hepatology (Baltimore, Md.) 12(2): 432	- Conference abstract
Perillo, RP; Regenstein, FG; Peters, MG (1989) Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis: a randomized, controlled trial. Genitourinary medicine 65(2): 141	- Full text paper not available
Perrillo, R, Davis, O, Bodenheimer, H et al. (1987) A randomized, controlled multicenter trial of recombinant interferon alfa-2b (rIFN-alfa), alone and following prednisone withdrawal, in	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
chronic type B hepatitis. Hepatology (Baltimore, Md.) 7(5): 1148	
Perrillo, R, Regenstein, F, Peters, M et al. (1986) Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic hepatitis B. Hepatology (Baltimore, Md.) 6(5): 1129	- Conference abstract
Perrillo, R, Schiff, E, Davis, GL et al. (1989) Multicenter randomized controlled trial of recombinant alpha interferon (rIFNa 2-b), alone or following prednisone withdrawal, in chronic hepatitis B (CHB). Hepatology (Baltimore, Md.) 10(4): 579	- Conference abstract
Pincus, T, Swearingen, C J, Luta, G et al. (2009) Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: a randomised, double-blind, placebo controlled withdrawal clinical trial. Annals of the rheumatic diseases 68(11): 1715-20	- Study does not contain an intervention relevant to this review protocol
Polito, Andrea; Aboab, Jerome; Annane, Djillali (2006) Adrenal insufficiency in sepsis. Revista Brasileira de terapia intensiva 18(1): 86-94	- Review article but not a systematic review
Ponticelli, C; Tarantino, A; Montagnino, G (2001) Steroid withdrawal in renal transplant recipients. Transplantation proceedings 33(12): 987-8	- Review article but not a systematic review
Price, DB, Rouleau, MY, Fletcher, CP et al. (2001) Use of montelukast in tapering inhaled corticosteroid therapy: an open-label, 48-week trial. Current therapeutic research, clinical and experimental 62(11): 743-755	- Study design not relevant to this review protocol
Quin, SM, Li, XM, Guo, YD et al. (1988) Prednisone withdrawal followed by poly I: c on chronic type B hepatitis - a double-blind randomized trial. Hepatology (Baltimore, Md.) 8(5): 1270	- Conference abstract
Rabe KF, Nair P, Brusselle G et al. (2018) Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. The New England journal of medicine 378(26): 2475-2485	- No useable outcome data
Raine, Charles, Stapleton, Philip P, Merinopoulos, Dimos et al. (2018) A 26-week feasibility study comparing the efficacy and safety of modified-release prednisone with immediate-release prednisolone in newly diagnosed cases of giant cell arteritis.	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
International journal of rheumatic diseases 21(1): 285-291	
Ratcliffe, P J, Firth, J D, Higgins, R M et al. (1993) Randomized controlled trial of complete steroid withdrawal in renal transplant patients receiving triple immunosuppression. Transplantation proceedings 25(1pt1): 590	- Conference abstract
Reed, A, Pirsch, J D, Armbrust, M J et al. (1991) A comparison of donor-specific and random transfusions in living-related renal transplantation and their effect on steroid withdrawal. Transplantation proceedings 23(1pt2): 1321-2	- Study does not contain an intervention relevant to this review protocol
Richter, Bernd; Neises, Gudrun; Clar, Christine (2002) Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. Endocrinology and metabolism clinics of North America 31(3): 751-78	- Systematic review used as source of primary studies
Rigotti, P (2002) Patients with high cholesterol levels benefit most from early withdrawal of corticosteroids. Transplantation proceedings 34(5): 1797-8	- Comparator in study does not match that specified in this review protocol
Rodrigues, J.C., Collister, D., Archer, A. et al. (2017) The steroid tapering in ANCA vasculitis evaluation study (stave) 2: A systematic review and meta-analysis. Rheumatology (United Kingdom) 56(supplement3): iii103	- Conference abstract
Rodriguez Roisin, Robert and Arismendi, Ebymar (2015) Inhaled corticosteroids withdrawal in severe patients with chronic obstructive pulmonary disease: a wisdom decision?. Archivos de bronconeumologia 51(2): 57-58	- Review article but not a systematic review
Salmasian, H, Rohanizadegan, M, Banihosseini, S et al. (2010) Corticosteroid regimens for treatment of acute and chronic graft versus host disease (GvHD) after allogenic stem cell transplantation. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Salmela, K, Vanrentergham, Y, Van Hoof, JP et al. (2001) Efficacy and safety of three months of tacrolimus/steroids/MMF followed by a controlled withdrawal of steroids or MMF: results of a large, prospective, multicentre trial. American journal of transplantation 1(suppl1): 246	- Conference abstract
Sandrini, Silvio, Setti, Gisella, Bossini, Nicola et al. (2010) Early (fifth day) vs. late (sixth month)	- No useable outcome data

Study	Reason for exclusion
steroid withdrawal in renal transplant recipients treated with Neoral(R) plus Rapamune(R): four-yr results of a randomized monocenter study. Clinical transplantation 24(5): 669-77	
Sayiner A, Aytemur ZA, Cirit M et al. (2001) Systemic glucocorticoids in severe exacerbations of COPD. Chest 119(3): 726-730	- Study does not contain an intervention relevant to this review protocol *looks at 2 different treatment regimes but does not focus on withdrawal.*
Schena, FP, Vincenti, F, Paraskevas, S et al. (2006) Renal function and rejection incidence in de novo renal transplant patients randomized to steroid avoidance, steroid withdrawal or standard steroids. Journal of the American Society of Nephrology : JASN 17(abstracts): 69a	- Conference abstract
Schena, FP, Vincenti, F, Paraskevas, S et al. (2006) 12-month results of a prospective, randomized trial of steroid avoidance, steroid withdrawal and standard steroids in de novo renal transplant patients receiving cyclosporine, enteric-coated mycophenolate sodium (EC-MPS, myfortic®) and basiliximab. American journal of transplantation 6(suppl2): 84-85	- Conference abstract
Schluter, U, le Cessie, S, Lamers, CBHW et al. (2002) Budesonide does not facilitate prednisone tapering in Crohn´s disease. European journal of gastroenterology & hepatology 14(12): a64	- Conference abstract
See, S. and Rubin, S. (2003) Tapering inhaled steroids effective for chronic asthma. Journal of Family Practice 52(10): 748-751	- Comparator in study does not match that specified in this review protocol
Shapiro, R, Jordan, M L, Scantlebury, V P et al. (1998) Outcome after steroid withdrawal in renal transplant patients receiving tacrolimus-based immunosuppression. Transplantation proceedings 30(4): 1375-7	- No useable outcome data reported
Sinha, Aditi, Saha, Abhijeet, Kumar, Manish et al. (2015) Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. Kidney international 87(1): 217-24	- Study does not contain an intervention relevant to this review protocol *looking at initial treatment protocols not withdrawal*
Skinner, J, Siddiqui, R, Gribbin, H et al. (1993) Steroid tapering in acute asthma. Lancet (London, England) 341(8847): 772	- Conference abstract

Study	Reason for exclusion
Sola, E, Alferez, M J, Cabello, M et al. (2002) Low-dose and rapid steroid withdrawal in renal transplant patients treated with tacrolimus and mycophenolate mofetil. Transplantation proceedings 34(5): 1689-90	- Comparator in study does not match that specified in this review protocol
Song, Tu-Run, Jiang, Ya-Mei, Liu, Jin-Peng et al. (2019) Steroid withdrawal or avoidance is safe in high-risk kidney transplants: A systematic review and meta-analysis. The Kaohsiung journal of medical sciences 35(6): 350-357	- Systematic review used as source of primary studies
Spiera, Robert, Unizony, Sebastian H, Bao, Min et al. (2021) Tocilizumab vs placebo for the treatment of giant cell arteritis with polymyalgia rheumatica symptoms, cranial symptoms or both in a randomized trial. Seminars in arthritis and rheumatism 51(2): 469-476	- Secondary publication of an included study that does not provide any additional relevant information
Sprung, C.L. (2009) The use of steroids in septic patients. Acta Anaesthesiologica Scandinavica, Supplement 53(119): 22-23	- Conference abstract
Squifflet, Jean-Paul, Vanrenterghem, Y, van Hooff, J P et al. (2002) Safe withdrawal of corticosteroids or mycophenolate mofetil: results of a large, prospective, multicenter, randomized study. Transplantation proceedings 34(5): 1584-6	- No useable outcome data reported
Stegall, MD, Everson, GT, Wachs, M et al. (1996) Prednisone withdrawal 14 days after adult liver transplantation with mycophenolate mofetil (MM). Hepatology (Baltimore, Md.) 24(4pt2): 174a	- Conference abstract
Stone, J., Bao, M., Han, J. et al. (2019) Long-term outcome of tocilizumab for patients with giant cell arteritis: Results from part 2 of a randomized controlled phase 3 trial. Arthritis and Rheumatology 71(supplement10): 1389-1390	- Conference abstract
Stone, J., Spotswood, H., Unizony, S. et al. (2019) Time to flare in patients with new-onset versus relapsing giant cell arteritis treated with tocilizumab or placebo plus prednisone Tapering: 3-Year Results from a Randomized Controlled Phase 3 Trial. Arthritis and Rheumatology 71(supplement10): 3278-3280	- Conference abstract
Stone, J., Tuckwell, K., Dimonaco, S. et al. (2019) Effects of baseline prednisone dose on remission and disease flare in patients with giant cell arteritis treated with tocilizumab in a phase 3 randomized controlled trial.	- Conference abstract

Study	Reason for exclusion
Rheumatology (United Kingdom) 58(supplement2)	
Stone, J.H., Neumann, T., Spotswood, H. et al. (2020) Time to flare in patients with new-onset versus relapsing giant cell arteritis treated with tocilizumab or placebo plus predni-sone tapering: 3-year results from a randomized controlled phase 3 trial. Swiss Medical Weekly 150(suppl245): 5s	- Conference abstract
Stone, J.H., Tuckwell, K., Dimonaco, S. et al. (2019) Effects of baseline prednisone dose on remission and disease flare in patients with giant cell arteritis treated with tocilizumab in the giacta trial. Rheumatology (United Kingdom) 58(supplement3): iii34	- Conference abstract
Stone, J.H., Tuckwell, K., Dimonaco, S. et al. (2018) Effects of baseline prednisone dose on remission and disease flare in patients with giant cell arteritis treated with tocilizumab in a phase 3 randomized controlled trial. Arthritis and Rheumatology 70(supplement9): 3094-3095	- Conference abstract
Stone, John H, Spotswood, Helen, Unizony, Sebastian H et al. (2022) New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. Rheumatology (Oxford, England) 61(7): 2915-2922	- Secondary publication of an included study that does not provide any additional relevant information
Stone, John H, Tuckwell, Katie, Dimonaco, Sophie et al. (2017) Trial of Tocilizumab in Giant-Cell Arteritis. The New England journal of medicine 377(4): 317-328	- No useable outcome data
Stouten, V., Joly, J., De Cock, D. et al. (2017) Sustained effectiveness of methotrexate with step-down glucocorticoid remission induction (cobra slim) for early rheumatoid arthritis in a treat-to-target setting: 2-year results of the carera trial. Annals of the Rheumatic Diseases 76(supplement2): 147	- Conference abstract
Stouten, V., Joly, J., De Cock, D. et al. (2017) Sustained effectiveness after remission induction with methotrexate and step-down glucocorticoids in patients with early rheumatoid arthritis following a treat-to-target strategy after 2 years. Arthritis and Rheumatology 69(supplement10)	- Conference abstract
Stouten, V., Joly, J., Pazmino, S. et al. (2018) Long-term effectiveness of the cobra slim remission induction and treat to target strategy in patients with early rheumatoid arthritis lacking	- Conference abstract

Study	Reason for exclusion
classical markers of poor prognosis: 2 year results of the carera trial. Annals of the Rheumatic Diseases 77(supplement2): 67	
Strand, Vibeke, Dimonaco, Sophie, Tuckwell, Katie et al. (2019) Health-related quality of life in patients with giant cell arteritis treated with tocilizumab in a phase 3 randomised controlled trial. Arthritis research & therapy 21(1): 64	- Data not reported in an extractable format or a format that can be analysed *lest sq mean with no SD or other measure of variability*
ter Meulen, Cornelis G, van Riemsdijk, Iza, Hene, Ronald J et al. (2004) Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor alpha therapy: a prospective, randomized, multicenter study. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 4(5): 803-10	- No useable outcome data reported
Theiler-Schwetz, Verena and Prete, Alessandro (2023) Glucocorticoid withdrawal syndrome: what to expect and how to manage. Current opinion in endocrinology, diabetes, and obesity	- Review article but not a systematic review
Thierry A, Mourad G, Büchler M et al. (2012) Steroid avoidance with early intensified dosing of enteric-coated mycophenolate sodium: a randomized multicentre trial in kidney transplant recipients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 27(9): 3651-3659	- Comparator in study does not match that specified in this review protocol
Thompson, G.; Ryan, M.; Thompson, P. (2019) Sustained benefit from using low-dose mepolizumab in patients with chronic relapsing eosinophilic granulomatosis with polyangiitis (EGPA). Internal Medicine Journal 49(supplement4): 32	- Conference abstract
Thomusch, Oliver, Wiesener, Michael, Opgenoorth, Mirian et al. (2016) Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet (London, England) 388(10063): 3006-3016	- No useable outcome data reported
Trompeter, R.S.; Grenda, R.; Watson, A. (2009) Improved growth in pediatric kidney recipients after early steroid withdrawal: Daclizumab, tacrolimus (TAC) and mycophenolate mofetil (MMF) versus TAC, MMF and steroids (TWIST Study). American Journal of Transplantation 9(suppl2): 365	- Conference abstract

Study	Reason for exclusion
Ueda, N, Chihara, M, Kawaguchi, S et al. (1988) Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. The Journal of pediatrics 112(1): 122-6	- No useable outcome data reported
Unizony, S., Bao, M., Han, J. et al. (2019) Risk factors for treatment failure in patients with giant cell arteritis treated with tocilizumab plus prednisone versus prednisone Alone. Arthritis and Rheumatology 71(supplement10): 3282-3284	- Conference abstract
Unizony, Sebastian H, Bao, Min, Han, Jian et al. (2021) Treatment failure in giant cell arteritis. Annals of the rheumatic diseases 80(11): 1467-1474	- Secondary publication of an included study that does not provide any additional relevant information
van As, A, Noonan, M, Kellerman, DJ et al. (1991) Asthma exacerbation following beclomethasone BD withdrawal. Annals of allergy 66: 79	- Conference abstract
van Hooff, JP, Vanrenterghem, Y, Squifflet, JP et al. (2001) First, large, prospective study of a controlled withdrawal of steroids or MMF following three months of tacrolimus/MMF/steroid therapy. Journal of the American Society of Nephrology : JASN 12(programabstracts): 920A-921A	- Full text paper not available
van Ouwerkerk, Lotte, Palmowski, Andriko, Nevins, Isabell S et al. (2022) Systematic literature review of observational cohorts and clinical trials into the success rate of glucocorticoid discontinuation after their use as bridging therapy in patients with rheumatoid arthritis. Annals of the rheumatic diseases 81(7): 937-943	- Systematic review used as source of primary studies
Vanrenterghem Y, Lebranchu Y, Hené R et al. (2000) Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. Transplantation 70(9): 1352-1359	- Comparator in study does not match that specified in this review protocol
Verschueren, P., De Cock, D., Corluy, L. et al. (2015) Remission induction with DMARD combinations and glucocorticoids is not superior to remission induction with mtx monotherapy and glucocorticoids: Week 52 results of the high-risk group from the carera trial. Annals of the Rheumatic Diseases 74(suppl2): 139	- Conference abstract
Verschueren, P, De Cock, D, Corluy, L et al. (2017) Effectiveness of methotrexate with step-	- No useable outcome data reported

Study	Reason for exclusion
down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Annals of the rheumatic diseases 76(3): 511-520	
Verschueren, P, De Cock, D, Corluy, L et al. (2015) Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. Annals of the rheumatic diseases 74(1): 27-34	- No useable outcome data reported
Vincenti, F, Schena, FP, Paraskevas, S et al. (2006) Metabolic effects of steroid avoidance or early steroid withdrawal: 12-month results of a randomized trial in de novo renal transplant patients receiving cyclosporine, enteric-coated mycophenolate sodium (EC-MPS) and basiliximab. American journal of transplantation 6(suppl2): 483	- Conference abstract
Vincenti, F, Monaco, A, Grinyo, J et al. (2001) Rapid steroid withdrawal versus standard steroid therapy in patients treated with basiliximab, cyclosporine, and mycophenolate mofetil for the prevention of acute rejection in renal transplantation. Transplantation proceedings 33(12): 1011-2	- No useable outcome data reported
Vincenti, F, Schena, F P, Paraskevas, S et al. (2008) A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 8(2): 307-16	- No useable outcome data reported
Vincenti, Flavio, Monaco, Anthony, Grinyo, Joseph et al. (2003) Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 3(3): 306-11	- No useable outcome data reported
Volkmann, E.R., Rezai, S., Tarp, S. et al. (2013) We still don't know how to taper glucocorticoids in rheumatoid arthritis, and we can do better. Journal of Rheumatology 40(10): 1646-1649	- Review article but not a systematic review

Study	Reason for exclusion
Watz, H., Calverley, P., Chanez, P. et al. (2014) The impact of stepwise withdrawal of inhaled corticosteroids on lung function in COPD patients receiving dual bronchodilation: WISDOM study. European Respiratory Journal 44(suppl58)	- Comparator in study does not match that specified in this review protocol
Webb, N., Douglas, S., Rajai, A. et al. (2014) Corticosteroid free immunosuppression is associated with continuing improved growth in young children following kidney transplantation; long term follow-up results from the twist randomised controlled trial. Pediatric Nephrology 29(9): 1683	- No useable outcome data reported
Webb, N, Trompeter, R, Cummins, C et al. (2013) Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind trial. PREDNOS clinical trial protocol version 2 1	- Study design not relevant to this review protocol
Webb, Nicholas J A, Douglas, Sarah E, Rajai, Azita et al. (2015) Corticosteroid-free Kidney Transplantation Improves Growth: 2-Year Follow-up of the TWIST Randomized Controlled Trial. Transplantation 99(6): 1178-85	- No useable outcome data reported
Webb, Nicholas J A, Woolley, Rebecca L, Lambe, Tosin et al. (2019) Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. BMJ (Clinical research ed.) 365: l1800	- Study does not contain an intervention relevant to this review protocol
Wechsler, Michael E, Colice, Gene, Griffiths, Janet M et al. (2020) SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. Respiratory research 21(1): 264	- No useable outcome data reported
Weiler, N., Hoppe-Lotichius, M., Zimmermann, T. et al. (2010) Early steroid-free immunosuppressive therapy with FK 506 after liver transplantation-5-year results of a prospective randomized double-blinded placebo-controlled study. Transplantation 90(suppl1): 33	- Conference abstract
Weimert, N, Alloway, R, Vinks, A et al. (2008) A 12-month, prospective, randomized, single center, open label pilot study to evaluate the	- Conference abstract

Study	Reason for exclusion
safety and efficacy of Myfortic® in combination with tacrolimus and thymoglobulin® in early corticosteroid withdrawal. Transplantation 86(2s): 36	
Wlodarczyk, Z, Glyda, M, Paczek, L et al. (2004) Long-term results of steroid withdrawal following renal transplantation in tacrolimus-based immunosupressioin regimens - results of multicenter study. 3rd international congress on immunosuppression; 2004 dec 8-11; san diego (CA)	- Full text paper not available
Woodle, E S (1999) Corticosteroid withdrawal in renal transplantation. Transplantation proceedings 31(12): 247-8	- Review article but not a systematic review
Woodle, E Steve, First, M Roy, Pirsch, John et al. (2008) A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Annals of surgery 248(4): 564-77	- Comparator in study does not match that specified in this review protocol
Woodle, ES (2003) A prospective, randomized, double blind, multicenter trial of early (7 day) corticosteroid cessation vs long term low dose corticosteroid therapy under tacrolimus and mycophenolate mofetil therapy with antibody induction. American journal of transplantation 3(suppl5): 198	- Conference abstract
Woodle, ES (2004) A prospective, randomized, double blind, placebo controlled multicenter study of early (7 day) corticosteroid cessation vs. long term low dose corticosteroid therapy under tacrolimus and mycophenolate mofetil therapy with antibody induction in renal transplant recipients. 3rd international congress on immunosuppression; 2004 dec 8-11; san diego (CA)	- Conference abstract
Wouters, E F M, Postma, D S, Fokkens, B et al. (2005) Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax 60(6): 480-7	- Study does not contain an intervention relevant to this review protocol
Wright, Linda S (2014) Steroid Withdrawal or Avoidance after Kidney Transplant. Nephrology nursing journal : journal of the American Nephrology Nurses' Association 41(6): 613-7	- Review article but not a systematic review
Wu, LW, Guo, ZY, Tai, Q et al. (2012) Steroid elimination within 24 hours after orthotopic liver transplantation: effectiveness and tolerability.	- Study design not relevant to this review protocol

Study	Reason for exclusion
Hepatobiliary & pancreatic diseases international 11(2): 137-142	
Yacyshyn, B R, Chey, W Y, Goff, J et al. (2002) Double blind, placebo controlled trial of the remission inducing and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, alicaforsen (ISIS 2302), in active steroid dependent Crohn's disease. Gut 51(1): 30-6	- Study does not contain an intervention relevant to this review protocol
Yadav, Menka, Sinha, Aditi, Khandelwal, Priyanka et al. (2019) Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Pediatric nephrology (Berlin, Germany) 34(5): 829-835	- Study does not contain an intervention relevant to this review protocol
Yao, GB; Fei, GZ; Zhang, LM (1991) Steroid withdrawal and recombinant interferon alpha in the treatment of chronic active hepatitis B. Chinese journal of digestion 11(3): 133-136	- Full text paper not available
Yates, M., Loke, Y., Watts, R. et al. (2012) Systematic review of steroid trials in giant cell arteritis. Rheumatology (United Kingdom) 51(suppl3): iii183	- Conference abstract
Ye, Wenjing, Guo, Xuejun, Yang, Tianyun et al. (2018) Systematic review of inhaled corticosteroid withdrawal effects in chronic obstructive pulmonary disease, and comparison with two "real-life" studies. Journal of thoracic disease 10(7): 4565-4573	- Systematic review used as source of primary studies
Zaghiyan, Karen, Melmed, Gil Y, Berel, Dror et al. (2014) A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Annals of surgery 259(1): 32-7	- Study does not contain an intervention relevant to this review protocol
Zhang, Huanxi, Zheng, Yitao, Liu, Longshan et al. (2016) Steroid Avoidance or Withdrawal Regimens in Paediatric Kidney Transplantation: A Meta-Analysis of Randomised Controlled Trials. PloS one 11(3): e0146523	- Systematic review used as source of primary studies
Zhang, Xin, Huang, Hejing, Han, Shu et al. (2013) Is it safe to withdraw steroids within seven days of renal transplantation?. Clinical transplantation 27(1): 1-8	- Systematic review used as source of primary studies
Zhu, Wei, Ye, Lei, Shen, Liyun et al. (2014) A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with graves' ophthalmopathy. The	- Study does not contain an intervention relevant to this review protocol

Study	Reason for exclusion
Journal of clinical endocrinology and metabolism 99(6): 1999-2007	
Zion, E., Borovitz, Y., Alfandary, H. et al. (2022) A Clinical Response-Adjusted Steroid Treatment Protocol for Children With Newly Diagnosed Idiopathic Nephrotic Syndrome. American Journal of Kidney Diseases 80(4): 473-482e1	- Study design not relevant to this review protocol

J.2 Health Economic studies

None.

Appendix K Recommendation for research

K.1 Research question

In people at risk of adrenal insufficiency because of prolonged corticosteroid use, what is the best way to manage corticosteroid withdrawal when corticosteroids are no longer needed to control underlying disease activity?

K.1.1 Why this is important.

There are over 900 000 prescriptions for exogenous glucocorticoids (GC) in the NHS a year. These including oral GC (hydrocortisone, prednisolone, and dexamethasone), inhaled, topical and intra articular/intramuscular GC used in the management of non- endocrine disorders such as inflammatory processes in rheumatology, gastroenterology, neurology, respiratory medicine and as an antiemetic in oncology. In oncology dexamethasone is frequently given cyclically every 1-3 weeks. Doses greater than or equivalent to 3-5mg prednisone a day for over 4 weeks suppress the hypothalamo-pituitary-adrenal axis putting the patient at risk of adrenal insufficiency. Some additional drugs potentiate the effect of GC to do this including antiretrovirals and antifungals.

Every team has its own method to taper GC medication doses with a view to stopping GC therapy. It is not clear which is the most effective way to do this, and if any methods are associated with less risk of long-term adrenal insufficiency. Also, with repeated courses in oncology it is not clear the impact of this or what to do when cyclical dexamethasone ends. Is likely duration, dose, and pharmacodynamics of treatment with GC that determines risk of adrenal insufficiency.

K.1.2 Rationale for the recommendation for research

Importance to 'patients' or the population	Uncertainty around how to withdraw glucocorticoids can lead to over treatment and increased risk of adrenal insufficiency. Patients can feel tired and unwell when withdrawing GC. This can lead to inappropriate testing of adrenal function and also, referrals to endocrinology. If there were clear guidelines, GC withdrawal could be managed more effectively.
Relevance to NICE guidance	As noted in the current guideline there is little evidence to support the recommendations on withdrawal of GC. Therefore, research will provide data to inform future guidance. It may also show that there are no concerns over any method of steroid withdrawal but help to give principles of who may be at risk of adrenal insufficiency after GC withdrawal.
Relevance to the NHS	As described above there are a lot of people on exogenous steroids for immune or inflammatory conditions. We do not know how to manage them optimally when it comes to withdrawing GC.
National priorities	This links in to the National Patient Safety Alert as an identified patient safety concern https://www.england.nhs.uk/publication/national-patient-safety-alert-steroid-emergency-card-to-support-early-recognition-and-treatment-of-adrenal-crisis-in-adults/.
Current evidence base	Minimal data. Bel 2014 looked indirectly with glucocorticoid withdrawal but did not specify information about patients able to discontinue GC. The other studies in this review were short term and so didn't provide evidence needed.
Equality considerations	None known.

K.1.3 Modified PICO table

Population	Defined groups of patients with varying underlying inflammatory conditions (? Nephrotic syndrome, lung sarcoidosis, inflammatory arthritis etc). To include children and elderly too.
Intervention	Stepwise withdrawal of prednisolone with alternate day dosing (predetermined weight-related dose reductions)
Comparator	Stepwise withdrawal of prednisolone with daily dosing
Outcome	Time to and proportion achieving full steroid withdrawal
Study design	Parallel groups, randomised
Timeframe	
Additional information	None