Supplementary Table 1: Clinical questions

Clinical question	Search criteria			Papers included (*n*)
	Population	**Predictor(s)**	**Outcome**	
Question I: What is the incidence of recovery of HPA axis in patients with glucocorticoid induced adrenal insufficiency?	Adult patients with glucocorticoid induced adrenal insufficiency	-	Incidence of HPA axis recovery, assessed by biochemical testing	2
Sub-question Ia: What clinical/biochemical parameters predict recovery of HPA axis in patients with glucocorticoid induced adrenal insufficiency?	Adult patients with glucocorticoid induced adrenal insufficiency	Clinical/biochemical parameters	HPA axis recovery, assessed by biochemical testing	2

Clinical question	Search criteria				Papers included (*n*)
	Population	**Intervention**	**Comparison**	**Outcome**	
Question II: What is the optimal tapering scheme in patients no longer requiring chronic glucocorticoid treatment for the underlying condition?	Adult patients on glucocorticoid therapy at risk for, or confirmed glucocorticoid induced adrenal insufficiency	Tapering scheme A	Tapering scheme B (or C etc) NB where ”tapering” might be ”abrupt withdrawal”	“Success rate” (i.e. successfully stop glucocorticoids completely without adrenal-related adverse event), adrenal crisis, adrenal insufficiency (biochemical), adrenal insufficiency (symptoms: hyponatremia, fatigue, weakness, weight loss, abdominal discomfort, nausea, vomiting, diarrhea), QoL, mortality, hospitalization, cost effectiveness	4

Clinical question	**Search criteria**				**Papers included (*n*)**
	Population	**Intervention**	**Reference standard**	**Outcome**	
Question III: What is the diagnostic accuracy of a morning cortisol value vs. 250 µg ACTH (1-24)-test in diagnosing glucocorticoid induced adrenal insufficiency in patients?	Adult patients on/directly after glucocorticoid therapy	Cortisol value	250 µg ACTH (1-24)-test	Diagnostic accuracy of diagnosing glucocorticoid induced adrenal insufficiency (sensitivity, specificity, PPV, NPV)	3
HPA = hypothalamic-pituitary-adrenal, QoL = quality of life, PPV = positive predictive value, NPV = negative predictive value					

Supplementary Table 2: GRADE evidence table

Questions:

What is the incidence of recovery of HPA axis in patients with glucocorticoid induced adrenal insufficiency?

What clinical/biochemical parameters predict recovery of HPA axis in patients with glucocorticoid induced adrenal insufficiency?

Certainty assessment							Importance
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	
77 (2 observational studies)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	IMPORTANT

Explanations

a. There were concerns regarding the domains 'study participation', 'study attrition' and 'adjustment for other prognostic factors'.
b. There were concerns regarding the wide 95% confidence interval and the small number of subjects.

Supplementary Table 3: Details of included studies

Study (year) - Design	**Population (*n*)**	**Sex M/F**	**Age mean (range)**	**GC therapy**	**Treatment dose mean (range) in mg/day**	**Treatment duration mean (range) in days**	**Adrenal function test - Definition of recovery**	**Time between retesting (months)**	***n* recovery at retesting (%)**	**Predictors of recovery**
Baek (2016) - Cohort	Patients with established GC-induced AI due to exogenous GC exposure for rheumatologic, orthopedic or chronic lung disease, or cancer chemotherapy (34)	14/20	69.5 (60.5 – 75.3)	Unknown*	Median 5 (2.5 - 10) after diagnosis of GC induced AI	Unknown	250 µg ACTH(1-24)-test - Peak stimulated cortisol level ≥ 500 nmol/L$^{\Delta}$	Median 16 (IQR 14-20)	20/34 (58.8) [95%CI 0.42-0.76]	Δ cortisol (cortisol increment at first 250 µg ACTH(1-24)-test): 219 (recovered group) *vs*. 99 nmol/L (non-recovered group)$^{\Delta}$, $p < 0.05$ OR 1.58 [95%CI 1.02-2.46] Cut-off for HPA axis recovery 226 nmol/L$^{\Delta}$ (sensitivity 50%/specificity 79%) and 250 nmol/L$^{\Delta}$ (sensitivity 40%/specificity 86%)
Leong (2018) - Cohort	Patients with established GC-induced AI due to exogenous GC exposure > 3 months, for	13/20	64.0 ± 1.8^	Oral GCs**	Last cumulative daily dose 13.4 ± 0.7^ - *dose only for hydrocortisone*	Median 720 (120-3600)	250 µg ACTH(1-24)-test - Peak stimulated cortisol level ≥ 503 nmol/L$^{\Delta}$	Retesting every 12 months until recovery, median recovery time 24 (3-49)	20/33 (58.8) [95%CI 0.44-0.78]	Ambulatory early morning cortisol: 286 (recovered group) *vs*. 186 nmol/L (non-

	dermatologic, renal or rheumatologic disease (20%) or obtained from traditional healers (80%) (33)									recovered group)$^{\Delta}$, *p* <0.01 OR 1.02 [95%CI 1.01-1.04] Cut-off for HPA axis recovery 244 nmol/L$^{\Delta}$ (sensitivity 70%/specificity 93%)

GC = glucocorticoid, AI = adrenal insufficiency, HPA = hypothalamic-pituitary-adrenal
OR = Odds ratio, 95%CI = 95% confidence interval
* after diagnosis of GC induced AI, patients were replaced with prednisone
** after diagnosis of GC induced AI, patients were replaced with hydrocortisone
$^{\Delta}$ converted from µg/dL to nmol/L by factor 27,78 (1.8 µg/dL = 50 nmol/L)
^ no range reported

Supplementary Table 4: GRADE evidence table

Question: What is the optimal tapering scheme in patients no longer requiring chronic glucocorticoid treatment for the underlying condition?

Certainty assessment							Importance
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	
266 (4 randomised trials)	not serious	not serious	serious[a]	not serious	not serious	⨁⨁⨁⨁ High	IMPORTANT

Explanations

a. In three studies, data on (serious) adverse events and hospital readmission were used as a proxy for symptomatic adrenal insufficiency/adrenal crisis

Supplementary Table 5: Details of included studies

Study (year) - design	**Population/indication for glucocorticoid therapy (*n*)**	**Sex M/F**	**Age mean (range)**	**Intervention (*n*)**	**Duration of follow-up**	**Outcome of interest**	**Outcome of interest: number of events**
Bazi (2021) - RCT	Moderate to severe multiple sclerosis relapse (66)	24/42	I: 33 ± 8.5^ II: 33 ± 6.9^	After treatment with intravenous methylprednisolone pulse 1 g/day for 5 days: I: oral prednisolone 50 mg/day, tapered-off with a 25% decrease at a five-day interval over 20 days (34) II: placebo (32)	24 weeks	Serious adverse events	I: 0 [one-sided 97.5%CI 0-0.05] II: 0 [one-sided 97.5%CI 0-0.05]
Burmester (2020) - RCT *only subgroup with prednisone tapering included*	Rheumatoid arthritis with stable low disease activity, receiving tocilizumab and glucocorticoids 5-15 mg/day for ≥ 24 weeks, of which prednisone 5mg/day for ≥ 4 weeks (131)	28/103	54.8 ± 14.0^	Taper prednisone with 1mg/day per 4 weeks, reaching 0 mg per day at 16 weeks (131)	24 weeks	Symptomatic adrenal insufficiency	0 [one-sided 97.5%CI 0-0.03]
O'Driscoll (1993) - RCT	Hospital admission with acute asthma (35)	17/18	I: 28 (18-55) II: 37 (20-53)	After treatment with prednisolone 40 mg/day for 10 days: I: oral prednisolone 5 mg/day, reducing from 7 tablets on day 11 to no tablets on day 18 (18)* II: placebo (17)*	28 days	Hospital readmission	I: 0 [one-sided 97.5%CI 0-0.10] II: 0 [one-sided 97.5%CI 0-0.10]

Sayiner (2000) - RCT	Hospital admission with respiratory failure due to severe COPD exacerbation (34)	32/2	I: 64.1 ± 2.2^ II: 67.4 ± 1.4^	After treatment with intravenous methylprednisolone 0,5 mg/kg/6h for 3 days: I: 0,5 mg/kg/12h for 3 days, 0,5 mg/kg/day for 4 days (17) II: placebo (17)	24 weeks	Adverse events	I: 0 [one-sided 97.5%CI 0-0.10] II: 0 [one-sided 97.5%CI 0-0.10]
^ no range reported * all patients continued inhaled glucocorticoids 97.5%CI = 97.5% confidence interval							

Supplementary Table 6: GRADE evidence table

Question: What is the diagnostic accuracy of a morning cortisol value *vs*. 250 µg ACTH (1-24)-test in diagnosing glucocorticoid induced adrenal insufficiency?

Certainty assessment							Importance
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	
409 (3 cross-sectional (cohort type accuracy) studies)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	LIMITED IMPORTANCE

Explanations

a. In two studies there were concerns regarding wide 95% confidence intervals and the relatively small number of subjects.

Supplementary Table 7: Details of included studies

Study (year) - Design	Population/ indication for GC therapy (*n*)	Test under study	Time between last GC dose and test (days)	Reference test - Definition of normal response	Cortisol measurement method	*n* AI (%)	Sensitivity	Specificity	PPV	NPV
Debono (2023) - Cohort	Receiving prednisolone-equivalent dose of ≥5 mg/day for ≥4 weeks, referred for adrenal testing after weaning down to prednisolone ≤5 mg/day or equivalent or converted to hydrocortisone ≤25 mg/d (139)◊	Baseline serum cortisol	1°	250 µg ACTH(1-24)-test - 30 minute stimulated cortisol level > 430 nmol/L	I Competitive immunoassay (electrochemiluminescence) II LC-MS/MS	I 66/139 (47.5%) II 68/139 (48.9%)	I Exclude AI: Cortisol ≥ 310 nmol/L 98.48% (95%CI 91.84, 99.96) Confirm AI: Cortisol <152 nmol/L 59.09% (95%CI 46.29, 71.05) (AUC 0.94 (0.9-0.97) II Exclude AI: Cortisol ≥ 327 nmol/L 98.53% (95%CI 92.08, 99.96) Confirm AI: Cortisol <152 nmol/L 57.35% (95%CI 44.77, 69.28) (AUC 0.92 (0.88-0.97)	I Exclude AI: Cortisol ≥ 310 nmol/L 47.95% (36.1, 59.96) Confirm AI: Cortisol <152 nmol/L 97.26% (95%CI 90.45, 99.67) (AUC 0.94 (0.9-0.97) II Exclude AI: Cortisol ≥ 327 nmol/L 39.44 (95%CI 28.03, 51.75) Confirm AI: Cortisol <152 nmol/L 97.18% (95%CI 90.19, 99.66) (AUC 0.92 (0.88-0.97)	I Exclude AI: Cortisol ≥ 310 nmol/L 63.11% (95%CI 53.03, 72.41) Confirm AI: Cortisol <152 nmol/L 95.12% (95%CI 83.47, 99.4) (AUC 0.94 (0.9-0.97) II Exclude AI: Cortisol ≥ 327 nmol/L 60.91 (95%CI 51.14, 70.07) Confirm AI: Cortisol <152 nmol/L 95.12% (95%CI 83.47, 99.4) (AUC 0.92 (0.88-0.97)	I Exclude AI: Cortisol ≥ 310 nmol/L 97.22% (85.47, 99.93) Confirm AI: Cortisol <152 nmol/L 72.45% (95%CI 62.5, 80.99) (AUC 0.94 (0.9-0.97) II Exclude AI: Cortisol ≥ 327 nmol/L 96.55 (95%CI 82.24, 99.91) Confirm AI: Cortisol <152 nmol/L 70.41% (95%CI 60.34, 79.21) (AUC 0.92 (0.88-0.97)
Sagar (2021) - Cohort	Rheumatologic disease, receiving GC therapy of prednisone equivalent ≥ 5 mg/day for ≥ 3 months (238)	Morning serum cortisol	1	250 µg ACTH(1-24)-test - 30 minute stimulated cortisol level > 450 nmol/L	Competitive immunoassay (chemiluminescence)	60/138 with SST (43.5)	Exclude AI: Cortisol > 350 nmol/L: 100%	Confirm AI: Cortisol < 100 nmol/L: 100%	-	-
Sbardella (2016) -	Disease different from endocrine conditions, receiving	Morning serum cortisol	n.r.	250 µg ACTH(1-24)-test -	Competitive immunoassay (chemiluminescence)	18 (56.3)	Exclude AI: Cortisol ≥ 336 nmol/L: 100%	Confirm AI: Cortisol ≤ 124 nmol/L: 100%	-	-

Cross-sectional	chronic GC therapy (32)*			30 minute stimulated cortisol level ≥ 430 nmol/L			(AUC 0.770, 95%CI 0.606 – 0.934)	(AUC 0.770, 95%CI 0.606 – 0.934)		

GC = glucocorticoid
AI = adrenal insufficiency
PPV = positive predictive value
NPV = negative predictive value
ACTH = adrenocorticotropic hormone
LC-MS/MS = liquid chromatography–tandem mass spectrometry
95%CI = 95% confidence interval
AUC = area under the curve
n.r. = not reported
◊ data for the cohort of glucocorticoid therapy users retrieved after contacting the authors
° ≥90 days after last injection for patients receiving any intermediate- or long-acting intramuscular or intra-articular glucocorticoid injections
* results of 3 different cortisol immunoassays were described, but only the results of the Abbott Architect assay were included here, since for this group Synacthen was administered both intravenous and intramuscular; for the other 2 groups only intramuscular