K.1 Research question:

What is the clinical and cost effectiveness of pharmacological treatments for the routine management of secondary and tertiary adrenal insufficiency?

K.1.1 Why this is important

Prednisolone and hydrocortisone are recommended as alternative pharmacological treatments in this guideline on the basis of current evidence. However, there are as yet no data directly comparing outcomes between these preparations, or with modified-release hydrocortisone, in this specific group. Gaining such evidence is important as there may be benefits of one pharmacological treatment over another. Restoration of a physiological circadian cortisol replacement schedule using modified-release hydrocortisone may reduce body mass index and improve glucose metabolism in patients with primary or secondary adrenal insufficiency, albeit that the number of patients previously studied is small. Conversely, prednisolone binds longer to the glucocorticoid receptor than hydrocortisone, which might lead to a prolonged clinical effect, improved adherence and reduced risk of adrenal crisis. Whether these theoretical differences lead to different clinical outcomes is unknown. Research to understand which glucocorticoid preparation is the more clinically effective in this population is therefore required. The health economic implications should also be addressed.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	This may provide evidence to change current care by recommending prednisolone, hydrocortisone or modified-release hydrocortisone as first-line treatment to people with secondary or tertiary adrenal insufficiency if one is proven to improve outcomes more than the other. This may improve outcomes and quality of life.
Relevance to NICE guidance	This question would potentially change guidance in terms of which corticosteroid preparation should be offered first-line in patients with secondary and tertiary adrenal insufficiency.
Relevance to the NHS	Potential impacts on the NHS include on service delivery in prehospital and hospital settings.
National priorities	None.
Current evidence base	
Equality considerations	In addition to the broader group of patients this research recommendation highlights the need for understanding corticosteroid use in specific subgroups (including but not exclusive to) people < 16 years of age.

K.1.3 Modified PICO table

Population	Inclusion: All adults and young people (>16 yrs) with established secondary or tertiary adrenal insufficiency. Stratified by: Aetiology • Adrenal insufficiency secondary to hypothalamic/pituitary disease • Adrenal insufficiency secondary to previous corticosteroid or opiate use On stable hydrocortisone replacement for at least 4 months

	On stable additional hormone replacement (thyroid hormone, oestrogen or testosterone, growth hormone) for at least 4 months Willing and able to provide written informed consent. Exclusion: Unable or unwilling to provide written informed consent. Pregnancy or breastfeeding
Intervention	Oral prednisolone and/or modified-release hydrocortisone
Comparison	Oral hydrocortisone
Outcomes	Disease-specific Quality of Life questionnaire (AddiQOL) Short Form-36 questionnaire EQ-5D Body weight Weight circumference Blood pressure Heart rate HbA1c Lipid profile Bone turnover markers Incidence of adrenal crises, infections and need for hospitalisation. Adverse events Outcomes measured at 1, 3 and 6 months.
Study design	RCT (potentially using a crossover design)
Timeframe	Medium term – in time for the next update
Additional information	None