

Chronic kidney disease

**[J] Evidence reviews for aspirational
haemoglobin target range for children and
young people with CKD**

NICE guideline NG203

*Evidence reviews underpinning recommendations 1.9.11 and
research recommendations in the NICE guideline*

August 2021

Final

*These evidence reviews were developed
by Guideline Updates Team*

Disclaimer

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Aspirational haemoglobin target range for children and young people with CKD

1.1 Review question

What should be the aspirational blood haemoglobin (Hb) target range for children and young people undergoing treatment for anaemia in CKD?

1.1.1 Introduction

Anaemia is a condition in which the quality or quantity of circulating red blood cells is below normal. A major cause of anaemia in chronic kidney disease (CKD) is a reduction in erythropoietin production due to kidney damage. Erythropoietin stimulates the bone marrow to produce red blood cells, and it is produced by the kidney in response to low tissue oxygen levels. Hb concentration serves as the key indicator for anaemia because it can be measured directly and has an international standard.

The 2015 NICE guideline on the management of anaemia in people with chronic kidney disease recommended that Hb should not normally be corrected to normal levels with erythropoiesis-stimulating agents (ESAs) in people with anaemia of CKD. The guideline also recommended maintaining the aspirational Hb range between 100 and 120g/litre for adults, young people and children aged 2 years and older and between 95 and 115g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group. During the scoping process this was highlighted as an area where there may be new evidence that would affect the current recommendations. This review aims to determine Hb range leads to the best outcomes for children and young people.

1.1.2 Summary of the protocol

Table 1: PICO table for aspirational haemoglobin target range for children and young people undergoing treatment for anaemia in CKD

Population	Children and young people with a clinical diagnosis of anaemia principally caused by CKD stages 1 to 5.
Intervention	Target Hb > 12 or Author defined 'high' Hb
Comparator	Hb < 12g/dl or Author defined standard
Outcomes	For the duration of follow up of the study: <ul style="list-style-type: none"> • All-cause mortality • Developmental milestone • Growth centile • CV specific mortality • QoL • Hypertension • Initiation of dialysis (in people not already on dialysis) • Adverse events

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 section in [Appendix B](#).

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search was carried out to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, which found 231 references (see [Appendix C](#) for the literature search strategy). These references were screened on their titles and abstracts. 17 studies were obtained and reviewed against the inclusion criteria as described in the review protocol ([Appendix A](#)). One study was identified as being relevant. See [Appendix D](#) for a PRISMA flow chart for study selection.

One crossover RCT was identified which included left ventricular mass index as an outcome. While this outcome was not specified in the review protocol, the committee was of the opinion that it was a clinically important outcome. Therefore, this evidence was included in the review and downgraded for indirectness.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 18 references for this review question, these were screened on title and abstract. One reference was ordered for full text screening. The reference was excluded based on its relevance to the review protocol ([Appendix A](#)).

See section [1.1.12 References – included studies](#) for a list of references for included studies.

1.1.4.2 Excluded studies

See [Appendix K](#) for a list of excluded studies with the primary reason for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

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

Short Title	Population	Interventions	Comparator	Outcome measure(s)
Morris 1993	Children with end stage renal failure and anaemia (n=11)	High Hb target 105-120 g/l (rHuEPO)	Low Hb target (Placebo) median 73g/l (range 42-81)	Left ventricular mass index (g/m ²) Follow-up: 48 weeks

See [Appendix E](#) for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Crossover randomised controlled trials (RCTs) were critically appraised using the Cochrane risk of bias tool (RoB 2.0) for crossover trials.

Table 3: Outcome: Left ventricular mass index (g/m²)

Comparison	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
High Hb target (rHuEPO) vs low Hb target (placebo)	7	MD 13.60 (-31.51, 58.71)	Very low ¹	Could not differentiate

¹This study was downgraded for risk of bias due to insufficient information on random sequence generation and allocation concealment. Additionally, baseline imbalances were present and there was insufficient information on the washout period. This study included data on left ventricular mass index, an outcome that was not specified in the review protocol. Therefore, this outcome was downgraded for being partially direct.

See [Appendix G](#) for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was conducted to identify economic evaluations relevant to the review question (see [Appendix C](#)). The search was not date limited. A total of 215 records were returned, 210 of which were excluded on the basis of title and abstract. The remaining 5 studies were fully inspected, and none were included in the synthesis. No additional studies were identified during inspection of the full publications and reference lists.

1.1.7.2 Excluded studies

Details of excluded studies are provided in [Appendix K](#).

1.1.8 Summary of included economic evidence

No economic evaluations relevant to the review question were found.

1.1.9 Economic model

No economic modelling was undertaken for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

No new studies examining the prespecified outcomes of interest were identified. However, one study was identified which included left ventricular mass index (LVMI) as an outcome. The committee agreed that this was a useful outcome measure as LVMI is a predictor of adverse cardiovascular events such as mortality, and given the lack of evidence for other outcomes, it agreed the study should be included.

1.1.10.2 The quality of the evidence

Overall, the quality of the evidence was very low. One crossover RCT was included in this review which presented several methodological limitations such as insufficient information on random sequence generation and allocation concealment, baseline imbalances and insufficient information on washout period. Furthermore, the study had a very small sample size and only 7 children completed both phases of the trial.

Additionally, the study only contributed one outcome of interest. While this outcome was not identified in the review protocol, the committee noted that it was a clinically useful measure and was used in practice. Therefore, the study was included but the outcome was downgraded for indirectness in its GRADE profile. Taking the lack of evidence and quality of evidence into consideration, the committee were unable to draft new recommendations of Hb levels in children and young people. However, they noted that further research was required in this area and therefore drafted a research recommendation which can help inform future updates.

1.1.10.3 Benefits and harms

The study included did not demonstrate any benefit. There was no difference between high and baseline Hb targets. The committee agreed that the evidence alone did not warrant an update of the 2014 guideline recommendations. Additionally, the committee noted that the

2014 guideline recommendations were in line with guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) which notes that using ESAs to achieve Hb levels greater than 120 g/litre is associated with an increased risk of death and serious cardiovascular events in people with CKD. In order to keep in line with drug safety guidance by the MHRA, the committee agreed to retain the recommendations from the 2014 guideline.

1.1.10.4 Cost effectiveness and resource use

No cost-effectiveness evidence was found. Since no new recommendations were made as part of this update, the committee did not expect any additional cost and resource impact.

1.1.10.5 Other factors the committee took into account

The committee also noted that while the current recommendations are line with MHRA guidance, which was based on two studies which did not include findings from a paediatric population or from young people. Furthermore, current NICE recommendations on optimal Hb levels for children and young people were based on the view that this population could in general be expected to benefit from similar Hb levels to adults.

However, the committee highlighted that coagulation risks in children and young people are very different to those in adults. The committee noted that the current recommended Hb levels may be too low for children as in practice higher targets of between 110 -130 g/litre are being used, but was unable to draft new recommendations about higher Hb levels because there was no new evidence. The committee agreed that further research in this area was important and highlighted that audit or registry data may also be useful as this would allow data on safety and efficacy to be captured for different Hb targets currently being used in practice. It made a research recommendation to support further research in this area.

1.1.11 Recommendations supported by this evidence review

No recommendations were made from this evidence review. Recommendation 1.9.11 was left unchanged and a research recommendation on the efficacy and safety of different aspirational Hb targets for children and young people with CKD undergoing treatment for anaemia was added (see [Appendix L](#) for further details about the research recommendation).

1.1.12 References – included studies

1.1.12.1 Effectiveness

Morris, K P, Skinner, J R, Hunter, S et al. (1993) Short term correction of anaemia with recombinant human erythropoietin and reduction of cardiac output in end stage renal failure.. Archives of disease in childhood 68(5): 644-8

1.1.12.2 Economic

None

Appendices

Appendix A – Review protocols

Review protocol for aspirational Hb target in anaemia of CKD

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Diagnosis and management of anaemia in CKD: what should be the aspirational Hb target range for children and young people undergoing treatment for anaemia in CKD?
2.	Review question	What should be the aspirational Hb target range for children and young people undergoing treatment for anaemia in CKD.
3.	Objective	To determine what Hb range leads to the best outcomes for children and young people.
4.	Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"> Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effect (DARE) Embase (Ovid) MEDLINE (Ovid) MEDLINE In-Process (Ovid) MEDLINE Epub Ahead of Print <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> English language Human studies <p>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>

ID	Field	Content
5.	Condition or domain being studied	Many people with CKD or established renal failure also develop associated anaemia. The prevalence of anaemia associated with CKD increases progressively with the stage of CKD, especially when the patient reaches stage 4 or 5. Anaemia of CKD contributes significantly to the burden of CKD. However, it is potentially reversible and manageable with appropriate identification and treatment.
6.	Population	Inclusion: Children and young people with a clinical diagnosis of anaemia principally caused by CKD stages 1 to 5. Exclusion: Adults Management of anaemia in people whose anaemia is not principally caused by CKD.
7.	Intervention	Target Hb > 12 or Author defined 'high' Hb
8.	Comparator	Hb < 12g/dl or Author defined standard
9.	Types of study to be included	RCTs SRs of RCTs
10.	Other exclusion criteria	Non-English language Abstracts and conference proceedings Theses Non-human studies
11.	Context	NICE guideline NG8 chronic kidney disease: managing anaemia will be updated by this question. This guideline will be combined with guidelines CG182 chronic kidney disease in adults: assessment and management and CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia.

ID	Field	Content
		The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.
12.	Primary outcomes (critical outcomes)	<p>For the duration of follow up of the study:</p> <ul style="list-style-type: none"> All-cause mortality Developmental milestone Growth centile CV specific mortality QoL Hypertension Initiation of dialysis (in people not already on dialysis) Adverse events
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	<p>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.</p> <p>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). Study investigators may be contacted for missing data where time and resources allow.</p>
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual .
16.	Strategy for data synthesis	<p>Meta-analyses of interventional data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).</p> <p>Fixed- and random-effects models (der Simonian and Laird) will be fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup</p>

ID	Field	Content														
		<p>analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met:</p> <p>Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis.</p> <p>The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.</p> <p>Meta-analyses will be performed in Cochrane Review Manager V5.3</p>														
17.	Analysis of sub-groups	<p>Where data allow, and if there is heterogeneity, the following subgroups analyses will be undertaken:</p> <p>Dialysis vs no-dialysis</p> <p>Male vs female</p> <p>Age range</p> <p>Actual Hb achieved</p> <p>Treatment</p>														
18.	Type and method of review	<table border="1"> <tr> <td data-bbox="833 753 1003 793"><input checked="" type="checkbox"/></td> <td data-bbox="1003 753 2047 793">Intervention</td> </tr> <tr> <td data-bbox="833 793 1003 833"><input type="checkbox"/></td> <td data-bbox="1003 793 2047 833">Diagnostic</td> </tr> <tr> <td data-bbox="833 833 1003 873"><input type="checkbox"/></td> <td data-bbox="1003 833 2047 873">Prognostic</td> </tr> <tr> <td data-bbox="833 873 1003 912"><input type="checkbox"/></td> <td data-bbox="1003 873 2047 912">Qualitative</td> </tr> <tr> <td data-bbox="833 912 1003 952"><input type="checkbox"/></td> <td data-bbox="1003 912 2047 952">Epidemiologic</td> </tr> <tr> <td data-bbox="833 952 1003 992"><input type="checkbox"/></td> <td data-bbox="1003 952 2047 992">Service Delivery</td> </tr> <tr> <td data-bbox="833 992 1003 1032"><input type="checkbox"/></td> <td data-bbox="1003 992 2047 1032">Other (please specify)</td> </tr> </table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic	<input type="checkbox"/>	Service Delivery	<input type="checkbox"/>	Other (please specify)
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<input type="checkbox"/>	Service Delivery															
<input type="checkbox"/>	Other (please specify)															
19.	Language	English														
20.	Country	England														
21.	Anticipated or actual start date	<p>[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins.</p> <p>A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]</p>														

ID	Field	Content																					
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]																					
23.	Stage of review at time of this submission	<table border="1"> <thead> <tr> <th>Review stage</th> <th>Started</th> <th>Completed</th> </tr> </thead> <tbody> <tr> <td>Preliminary searches</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> <tr> <td>Piloting of the study selection process</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> <tr> <td>Formal screening of search results against eligibility criteria</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> <tr> <td>Data extraction</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> <tr> <td>Risk of bias (quality) assessment</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> <tr> <td>Data analysis</td> <td><input type="checkbox"/> <input type="checkbox"/></td> <td><input type="checkbox"/> <input type="checkbox"/></td> </tr> </tbody> </table>	Review stage	Started	Completed	Preliminary searches	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	Piloting of the study selection process	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	Formal screening of search results against eligibility criteria	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	Data extraction	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	Risk of bias (quality) assessment	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	Data analysis	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
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Data analysis	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>																					
24.	Named contact	<p>5a. Named contact Guideline Updates Team</p> <p>5b Named contact e-mail [Guideline email]@nice.org.uk</p> <p>5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)</p>																					
25.	Review team members	<p>From the Guideline Updates Team:</p> <p>Mr Chris Carmona Dr Yolanda Martinez Ms Hannah Nicholas</p>																					

ID	Field	Content
		Ms Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.
27.	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.
28.	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
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	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. [Add in any additional agree dissemination plans.]
32.	Keywords	
33.	Details of existing review of same topic by same authors	
34.	Current review status	<input type="checkbox"/> Ongoing

ID	Field	Content	
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input type="checkbox"/>	Discontinued
35..	Additional information		
36.	Details of final publication		www.nice.org.uk

Appendix B – Methods

Evidence synthesis and meta- analyses

No meta-analysis was possible in this review because it only contained a single study. The included study was a crossover RCT and for the purposes of this systematic review only data from the first crossover period were extracted and used.

Evidence of effectiveness of interventions

Quality assessment

Crossover RCTs were quality assessed using the Cochrane Risk of Bias Tool for crossover trials (RoB 2.0)

Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Some concerns – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a MID to be defined to act as a non-inferiority margin. The same MIDs were used both to inform decision making and to measure imprecision in GRADE.

Since no other MID was available for the study included in this review, a MID of +/- 0.5 standard deviations from the mean value was used (see Norman 2003).

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes

consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in [Table 4](#).

Table 4: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.</p>
Indirectness	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.</p>
Inconsistency	<p>Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.</p> <p>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.</p> <p>Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.</p> <p>Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.</p> <p>Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.</p>
Imprecision	<p>If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.</p> <p>If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if</p>

GRADE criteria	Reasons for downgrading quality
	<p>the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.</p> <p>Outcomes were downgraded 2 levels if effect size could not be calculated.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.</p>

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed where 10 or more studies were included as part of a single meta-analysis and a funnel plot was produced to graphically assess the potential for publication bias.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in [Table 5](#).

Table 5: Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost

Level	Explanation
	effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in [Table 6](#).

Table 6: Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run on the 27th of June 2019 and updated between the 15th and 16th of September 2020. This search report is compliant with the requirements of [PRISMA-S](#).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the [2016 PRESS Checklist](#).

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences in Embase were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). [Systematic Reviews: Identifying relevant studies for systematic reviews](#). *BMJ*, 309(6964), 1286.

Clinical searches

Databases	Date searched	Version/files	No. retrieved	EPPI-R5 data
Cochrane Central Register of Controlled Trials (CENTRAL)	27 th June 2019	Issue 6 of 12, June 2019	88	42
Cochrane Database of Systematic Reviews (CDSR)	27 th June 2019	Issue 6 of 12, June 2019	8	2
Database of Abstracts of Reviews of Effect (DARE)	27 th June 2019	Up to 2015	32	30
Embase (Ovid)	27 th June 2019	Embase <1974 to 2019 Week 25>	124	62

MEDLINE (Ovid)	27 th June 2019	Ovid MEDLINE(R) ALL <1946 to June 26, 2019>	95	95
MEDLINE In-Process (Ovid)	27 th June 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 26, 2019>	3	0
MEDLINE Epub Ahead of Print^a	27 th June 2019	Ovid MEDLINE(R) Epub Ahead of Print <June 26, 2019>	2	0

The following search filters were applied in MEDLINE and Embase to identify RCTs and systematic reviews:

- RCT filters:
 - [McMaster Therapy – Medline](#) - “best balance of sensitivity and specificity” version.
Haynes RB et al. (2005) [Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey](#). *BMJ*, 330, 1179-1183.
 - [McMaster Therapy – Embase](#) “best balance of sensitivity and specificity” version.

Wong SSL et al. (2006) [Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE](#). *Journal of the Medical Library Association*, 94(1), 41-47.
- Systematic reviews filters:
 - Lee, E. et al. (2012) [An optimal search filter for retrieving systematic reviews and meta-analyses](#). *BMC Medical Research Methodology*, 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Search strategies
Database: Ovid MEDLINE(R) ALL <1946 to June 26, 2019>
Search Strategy:

1 exp Renal Insufficiency, Chronic/ (108136)

^a Please search for both development and re-run searches

- 2 ((chronic* or progressi*) adj1 (renal* or kidney*).tw. (79151)
- 3 ((kidney* or renal*) adj1 insufficien*).tw. (22147)
- 4 ckd*.tw. (25833)
- 5 ((kidney* or renal*) adj1 fail*).tw. (91631)
- 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*).tw. (38893)
- 7 (esrd* or eskd*).tw. (15633)
- 8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3385)
- 9 or/1-8 (225307)
- 10 exp Anemia/ (156463)
- 11 (anemi* or anaemi*).tw. (140887)
- 12 10 or 11 (218816)
- 13 9 and 12 (13867)
- 14 exp Hemoglobins/ (122231)
- 15 (haemoglobin* or hemoglobin* or hb or hgb).tw. (174051)
- 16 14 or 15 (222628)
- 17 13 and 16 (4146)
- 18 (MEDLINE or pubmed).tw. (177769)
- 19 systematic review.tw. (131097)
- 20 systematic review.pt. (108831)
- 21 meta-analysis.pt. (102276)
- 22 intervention\$.ti. (134941)
- 23 or/18-22 (406199)
- 24 randomized controlled trial.pt. (484558)
- 25 randomi?ed.mp. (825342)
- 26 placebo.mp. (205282)
- 27 or/24-26 (882194)
- 28 23 or 27 (1175980)
- 29 17 and 28 (703)
- 30 exp Infant/ or Infant Health/ or Infant Welfare/ (1100278)
- 31 (prematuro* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (897689)

- 32 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1841806)
- 33 Minors/ (2508)
- 34 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2547177)
- 35 exp pediatrics/ (55449)
- 36 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (894207)
- 37 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1941110)
- 38 Puberty/ (13001)
- 39 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (459391)
- 40 Schools/ (35244)
- 41 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8597)
- 42 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (514111)
- 43 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (4257)
- 44 or/30-43 (5424666)
- 45 29 and 44 (98)
- 46 limit 45 to english language (95)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 26, 2019>

Search Strategy:

-
- 1 exp Renal Insufficiency, Chronic/ (0)
- 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8871)
- 3 ((kidney* or renal*) adj1 insufficien*).tw. (1046)
- 4 ckd*.tw. (4255)
- 5 ((kidney* or renal*) adj1 fail*).tw. (6074)
- 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4453)
- 7 (esrd* or eskd*).tw. (1845)
- 8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)
- 9 or/1-8 (17418)
- 10 exp Anemia/ (0)

- 11 (anemi* or anaemi*).tw. (12189)
- 12 10 or 11 (12189)
- 13 9 and 12 (887)
- 14 exp Hemoglobins/ (0)
- 15 (haemoglobin* or hemoglobin* or hb or hgb).tw. (16653)
- 16 14 or 15 (16653)
- 17 13 and 16 (269)
- 18 (MEDLINE or pubmed).tw. (29319)
- 19 systematic review.tw. (23963)
- 20 systematic review.pt. (230)
- 21 meta-analysis.pt. (36)
- 22 intervention\$.ti. (18393)
- 23 or/18-22 (57325)
- 24 randomized controlled trial.pt. (276)
- 25 randomi?ed.mp. (65450)
- 26 placebo.mp. (16133)
- 27 or/24-26 (71242)
- 28 23 or 27 (115817)
- 29 17 and 28 (53)
- 30 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
- 31 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (70300)
- 32 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
- 33 Minors/ (0)
- 34 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (279689)
- 35 exp pediatrics/ (0)
- 36 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (104282)
- 37 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
- 38 Puberty/ (0)
- 39 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (51950)

- 40 Schools/ (0)
- 41 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
- 42 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (60720)
- 43 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (505)
- 44 or/30-43 (405899)
- 45 29 and 44 (3)
- 46 limit 45 to english language (3)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 26, 2019>

Search Strategy:

-
- 1 exp Renal Insufficiency, Chronic/ (0)
- 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1368)
- 3 ((kidney* or renal*) adj1 insufficien*).tw. (174)
- 4 ckd*.tw. (711)
- 5 ((kidney* or renal*) adj1 fail*).tw. (749)
- 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (691)
- 7 (esrd* or eskd*).tw. (331)
- 8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)
- 9 or/1-8 (2590)
- 10 exp Anemia/ (0)
- 11 (anemi* or anaemi*).tw. (1624)
- 12 10 or 11 (1624)
- 13 9 and 12 (137)
- 14 exp Hemoglobins/ (0)
- 15 (haemoglobin* or hemoglobin* or hb or hgb).tw. (2399)
- 16 14 or 15 (2399)
- 17 13 and 16 (51)
- 18 (MEDLINE or pubmed).tw. (6282)
- 19 systematic review.tw. (5803)

- 20 systematic review.pt. (15)
- 21 meta-analysis.pt. (4)
- 22 intervention\$.ti. (3788)
- 23 or/18-22 (12364)
- 24 randomized controlled trial.pt. (1)
- 25 randomi?ed.mp. (12583)
- 26 placebo.mp. (3014)
- 27 or/24-26 (13612)
- 28 23 or 27 (23086)
- 29 17 and 28 (9)
- 30 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
- 31 (prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (14221)
- 32 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
- 33 Minors/ (0)
- 34 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (49169)
- 35 exp pediatrics/ (0)
- 36 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (19252)
- 37 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
- 38 Puberty/ (0)
- 39 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (12647)
- 40 Schools/ (0)
- 41 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
- 42 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (11641)
- 43 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (90)
- 44 or/30-43 (72562)
- 45 29 and 44 (2)
- 46 limit 45 to english language (2)

Database: Embase <1974 to 2019 Week 25>

Search Strategy:

-
- 1 exp kidney failure/ (330779)
 - 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115064)
 - 3 ((kidney* or renal*) adj1 insufficien*).tw. (29268)
 - 4 ckd*.tw. (44929)
 - 5 ((kidney* or renal*) adj1 fail*).tw. (128105)
 - 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54766)
 - 7 (esrd* or eskd*).tw. (25497)
 - 8 or/1-7 (420393)
 - 9 exp anemia/ (334503)
 - 10 (anemi* or anaemi*).tw. (192311)
 - 11 9 or 10 (370954)
 - 12 8 and 11 (36885)
 - 13 exp hemoglobin/ (309665)
 - 14 hemoglobin blood level/ (61188)
 - 15 exp hemoglobin analysis/ (22911)
 - 16 (haemoglobin* or hemoglobin* or hb or hgb).tw. (246083)
 - 17 or/13-16 (403610)
 - 18 12 and 17 (10048)
 - 19 (MEDLINE or pubmed).tw. (223340)
 - 20 exp systematic review/ or systematic review.tw. (251529)
 - 21 meta-analysis/ (164798)
 - 22 intervention\$.ti. (180925)
 - 23 or/19-22 (578637)
 - 24 random:.tw. (1421873)
 - 25 placebo:.mp. (434360)
 - 26 double-blind:.tw. (198902)
 - 27 or/24-26 (1669891)
 - 28 23 or 27 (2067382)
 - 29 18 and 28 (1352)

- 30 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3246394)
- 31 (premat* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1142525)
- 32 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3412794)
- 33 exp pediatrics/ (99771)
- 34 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1532721)
- 35 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (97325)
- 36 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (612398)
- 37 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (97583)
- 38 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (650597)
- 39 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (6711)
- 40 or/30-39 (6066382)
- 41 29 and 40 (174)
- 42 limit 41 to english language (171)
- 43 limit 42 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (47)
- 44 42 not 43 (124)

Search Name: GU - CKD - eGFR_anaemia - Lynda

Date Run: 27/06/2019 18:13:25

Comment:

ID	Search Hits
#1	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 5944
#2	(((chronic* or progressi*) near/1 (renal* or kidney*))) :ti,ab,kw 9491
#3	(((kidney* or renal*) near/1 insufficien*)) :ti,ab,kw 4617
#4	(ckd*) :ti,ab,kw 4336
#5	(((kidney* or renal*) near/1 fail*)) :ti,ab,kw 15414

#6	((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*)):ti,ab,kw	4179
#7	((esrd* or eskd*)):ti,ab,kw	1907
#8	MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only	80
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	24140
#10	MeSH descriptor: [Anemia] explode all trees	4775
#11	(anemi* or anaemi*):ti,ab,kw	19047
#12	#10 or #11	19427
#13	#9 and #12	2263
#14	MeSH descriptor: [Hemoglobins] explode all trees	8875
#15	(haemoglobin* or hemoglobin* or hb or hgb):ti,ab,kw	45333
#16	#14 or #15	45522
#17	#13 and #16	1034
#18	MeSH descriptor: [Infant] explode all trees	15368
#19	MeSH descriptor: [Infant Health] this term only	37
#20	MeSH descriptor: [Infant Welfare] this term only	81
#21	((prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):ti,ab,kw	82210
#22	((prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):so	4793
#23	MeSH descriptor: [Child] explode all trees	1171
#24	MeSH descriptor: [Child Behavior] explode all trees	1898
#25	MeSH descriptor: [Child Health] this term only	79
#26	MeSH descriptor: [Child Welfare] this term only	320
#27	MeSH descriptor: [Minors] this term only	8
#28	((child* or minor or minors or boy* or girl* or kid or kids or young*)):ti,ab,kw	244543
#29	((child* or minor or minors or boy* or girl* or kid or kids or young*)):so	9784
#30	MeSH descriptor: [Pediatrics] explode all trees	632
#31	((pediatric* or paediatric* or peadiatric*)):ti,ab,kw	30581
#32	((pediatric* or paediatric* or peadiatric*)):so	30904
#33	MeSH descriptor: [Adolescent] this term only	99786
#34	MeSH descriptor: [Adolescent Behavior] this term only	1300

- #35 MeSH descriptor: [Adolescent Health] this term only 21
- #36 MeSH descriptor: [Puberty] this term only 298
- #37 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)):ti,ab,kw 133518
- #38 ((adolescen* or pubescen* or prepubescen* or pre-pubecen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or juvenil* or youth* or under*age*)):so 3576
- #39 MeSH descriptor: [Schools] this term only 1728
- #40 MeSH descriptor: [Child Day Care Centers] this term only 215
- #41 MeSH descriptor: [Nurseries] this term only 8
- #42 MeSH descriptor: [Schools, Nursery] this term only 36
- #43 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):ti,ab,kw 89461
- #44 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):so 1111
- #45 (("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*")):ti,ab,kw 14094
- #46 {or #18-#45} 388504
- #47 #17 and #46 189
- #48 "conference":pt or "clinicaltrials.gov":so or "www.who.int":so 407311
- #49 #47 not #48 96 (8 CDSR, 88 Central)

CRD databases

- | | | | |
|---|---|-----|--------|
| 1 | MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES | 538 | |
| | Delete | | |
| 2 | ((chronic* or progressi*) near1 (renal* or kidney*)) | 489 | Delete |
| 3 | ((kidney* or renal*) near1 insufficien*) | 320 | Delete |
| 4 | (ckd*) | 93 | Delete |
| 5 | ((kidney* or renal*) near1 fail*) | 836 | Delete |
| 6 | ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*)) | 354 | Delete |
| 7 | (esrd* or eskd*) | 150 | Delete |

8	MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder	0	Delete
9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	1407	Delete
10	MeSH DESCRIPTOR Anemia EXPLODE ALL TREES	380	Delete
11	(anemi* or anaemi*)	731	Delete
12	(#10 or #11)	791	Delete
13	MeSH DESCRIPTOR Hemoglobins EXPLODE ALL TREES	493	Delete
14	(haemoglobin* or hemoglobin* or hb or hgb)	1350	Delete
15	(#13 or #14)	1353	Delete
16	#9 AND #12 AND #15	56	Delete
17	(#16) IN DARE	32	Delete

Cost-effectiveness searches

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	27 th June 2019	Ovid MEDLINE(R) <1946 to June 26, 2019>	78
MEDLINE in Process (Ovid)	27 th June 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 26, 2019>	3
MEDLINE epub (Ovid)	27 th June 2019	Ovid MEDLINE(R) Epub Ahead of Print <June 26, 2019>	3
Embase (Ovid)	27 th June 2019	Embase <1974 to 2019 Week 25>	143
EconLit (Ovid)	27 th June 2019	Econlit <1886 to June 13, 2019>	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	27 th June 2019	Up to 2015	19

CRD HTA	27 th June 2019	Up to 2018	5

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) [Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE](#). Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Search strategies
Database: Ovid MEDLINE(R) <1946 to June 26, 2019>
Search Strategy:

1 exp Renal Insufficiency, Chronic/ (108136)
2 ((chronic* or progressi*) adj1 (renal* or kidney*).tw. (68907)
3 ((kidney* or renal*) adj1 insufficien*).tw. (20927)
4 ckd*.tw. (20864)
5 ((kidney* or renal*) adj1 fail*).tw. (84808)
6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*).tw. (33749)
7 (esrd* or eskd*).tw. (13457)
8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3385)
9 or/1-8 (205294)
10 exp Anemia/ (156463)
11 (anemi* or anaemi*).tw. (127070)
12 10 or 11 (204999)
13 9 and 12 (12843)
14 exp Hemoglobins/ (122231)
15 (haemoglobin* or hemoglobin* or hb or hgb).tw. (154992)
16 14 or 15 (203569)

- 17 13 and 16 (3826)
- 18 exp Infant/ or Infant Health/ or Infant Welfare/ (1100278)
- 19 (premat* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (813144)
- 20 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1841806)
- 21 Minors/ (2508)
- 22 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2218231)
- 23 exp pediatrics/ (55449)
- 24 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (770654)
- 25 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1941109)
- 26 Puberty/ (13001)
- 27 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (394776)
- 28 Schools/ (35244)
- 29 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8597)
- 30 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (441727)
- 31 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (3662)
- 32 or/18-31 (4946072)
- 33 17 and 32 (758)
- 34 Economics/ (27052)
- 35 exp "Costs and Cost Analysis"/ (225878)
- 36 Economics, Dental/ (1902)
- 37 exp Economics, Hospital/ (23661)
- 38 exp Economics, Medical/ (14105)
- 39 Economics, Nursing/ (3986)
- 40 Economics, Pharmaceutical/ (2865)
- 41 Budgets/ (11131)
- 42 exp Models, Economic/ (14213)
- 43 Markov Chains/ (13479)
- 44 Monte Carlo Method/ (26851)
- 45 Decision Trees/ (10597)

- 46 econom\$.tw. (220215)
- 47 cba.tw. (9562)
- 48 cea.tw. (19653)
- 49 cua.tw. (941)
- 50 markov\$.tw. (16711)
- 51 (monte adj carlo).tw. (28228)
- 52 (decision adj3 (tree\$ or analys\$)).tw. (12093)
- 53 (cost or costs or costing\$ or costly or costed).tw. (426999)
- 54 (price\$ or pricing\$).tw. (31190)
- 55 budget\$.tw. (22419)
- 56 expenditure\$.tw. (46208)
- 57 (value adj3 (money or monetary)).tw. (1940)
- 58 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw. (3347)
- 59 or/34-58 (867208)
- 60 "Quality of Life"/ (177793)
- 61 quality of life.tw. (209504)
- 62 "Value of Life"/ (5651)
- 63 Quality-Adjusted Life Years/ (11133)
- 64 quality adjusted life.tw. (9737)
- 65 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (8007)
- 66 disability adjusted life.tw. (2371)
- 67 daly\$.tw. (2179)
- 68 Health Status Indicators/ (22913)
- 69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21090)
- 70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1256)
- 71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4458)
- 72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)
- 73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (369)

- 74 (euroqol or euro qol or eq5d or eq 5d).tw. (7754)
- 75 (qol or hql or hqol or hrqol).tw. (39820)
- 76 (hye or hyes).tw. (58)
- 77 health\$ year\$ equivalent\$.tw. (38)
- 78 utilit\$.tw. (158380)
- 79 (hui or hui1 or hui2 or hui3).tw. (1205)
- 80 disutili\$.tw. (350)
- 81 rosser.tw. (82)
- 82 quality of wellbeing.tw. (11)
- 83 quality of well-being.tw. (367)
- 84 qwb.tw. (186)
- 85 willingness to pay.tw. (3934)
- 86 standard gamble\$.tw. (762)
- 87 time trade off.tw. (980)
- 88 time tradeoff.tw. (223)
- 89 tto.tw. (846)
- 90 or/60-89 (454682)
- 91 59 or 90 (1258924)
- 92 33 and 91 (90)
- 93 limit 92 to english language (78)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 26, 2019>

Search Strategy:

-
- 1 exp Renal Insufficiency, Chronic/ (0)
- 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8871)
- 3 ((kidney* or renal*) adj1 insufficien*).tw. (1046)
- 4 ckd*.tw. (4255)
- 5 ((kidney* or renal*) adj1 fail*).tw. (6074)
- 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4453)
- 7 (esrd* or eskd*).tw. (1845)

8	"Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)
9	or/1-8 (17418)
10	exp Anemia/ (0)
11	(anemi* or anaemi*).tw. (12189)
12	10 or 11 (12189)
13	9 and 12 (887)
14	exp Hemoglobins/ (0)
15	(haemoglobin* or hemoglobin* or hb or hgb).tw. (16653)
16	14 or 15 (16653)
17	13 and 16 (269)
18	exp Infant/ or Infant Health/ or Infant Welfare/ (0)
19	(prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (70300)
20	exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
21	Minors/ (0)
22	(child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (279689)
23	exp pediatrics/ (0)
24	(pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (104282)
25	Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
26	Puberty/ (0)
27	(adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (51950)
28	Schools/ (0)
29	Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
30	(pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (60720)
31	("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (505)
32	or/18-31 (405899)
33	17 and 32 (38)
34	Economics/ (0)
35	exp "Costs and Cost Analysis"/ (0)
36	Economics, Dental/ (0)

- 37 exp Economics, Hospital/ (0)
- 38 exp Economics, Medical/ (0)
- 39 Economics, Nursing/ (0)
- 40 Economics, Pharmaceutical/ (0)
- 41 Budgets/ (0)
- 42 exp Models, Economic/ (0)
- 43 Markov Chains/ (0)
- 44 Monte Carlo Method/ (0)
- 45 Decision Trees/ (0)
- 46 econom\$.tw. (38890)
- 47 cba.tw. (373)
- 48 cea.tw. (1636)
- 49 cua.tw. (168)
- 50 markov\$.tw. (4943)
- 51 (monte adj carlo).tw. (15268)
- 52 (decision adj3 (tree\$ or analys\$)).tw. (2002)
- 53 (cost or costs or costing\$ or costly or costed).tw. (83877)
- 54 (price\$ or pricing\$).tw. (5150)
- 55 budget\$.tw. (4432)
- 56 expenditure\$.tw. (5782)
- 57 (value adj3 (money or monetary)).tw. (319)
- 58 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw. (505)
- 59 or/34-58 (145483)
- 60 "Quality of Life"/ (0)
- 61 quality of life.tw. (34206)
- 62 "Value of Life"/ (0)
- 63 Quality-Adjusted Life Years/ (0)
- 64 quality adjusted life.tw. (1475)
- 65 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (1236)
- 66 disability adjusted life.tw. (442)
- 67 daly\$.tw. (400)

- 68 Health Status Indicators/ (0)
- 69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2441)
- 70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (654)
- 71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (653)
- 72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)
- 73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)
- 74 (euroqol or euro qol or eq5d or eq 5d).tw. (1485)
- 75 (qol or hql or hqol or hrqol).tw. (6493)
- 76 (hye or hyes).tw. (5)
- 77 health\$ year\$ equivalent\$.tw. (2)
- 78 utilit\$.tw. (27374)
- 79 (hui or hui1 or hui2 or hui3).tw. (158)
- 80 disutili\$.tw. (60)
- 81 rosser.tw. (13)
- 82 quality of wellbeing.tw. (6)
- 83 quality of well-being.tw. (27)
- 84 qwb.tw. (8)
- 85 willingness to pay.tw. (805)
- 86 standard gamble\$.tw. (53)
- 87 time trade off.tw. (107)
- 88 time tradeoff.tw. (10)
- 89 tto.tw. (115)
- 90 or/60-89 (63699)
- 91 59 or 90 (200905)
- 92 33 and 91 (3)
- 93 limit 92 to english language (3)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 26, 2019>

Search Strategy:

-
- 1 exp Renal Insufficiency, Chronic/ (0)
 - 2 ((chronic* or progressi*) adj1 (renal* or kidney*).tw. (1368)
 - 3 ((kidney* or renal*) adj1 insufficien*).tw. (174)
 - 4 ckd*.tw. (711)
 - 5 ((kidney* or renal*) adj1 fail*).tw. (749)
 - 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*).tw. (691)
 - 7 (esrd* or eskd*).tw. (331)
 - 8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)
 - 9 or/1-8 (2590)
 - 10 exp Anemia/ (0)
 - 11 (anemi* or anaemi*).tw. (1624)
 - 12 10 or 11 (1624)
 - 13 9 and 12 (137)
 - 14 exp Hemoglobins/ (0)
 - 15 (haemoglobin* or hemoglobin* or hb or hgb).tw. (2399)
 - 16 14 or 15 (2399)
 - 17 13 and 16 (51)
 - 18 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 - 19 (premat* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (14221)
 - 20 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 - 21 Minors/ (0)
 - 22 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (49169)
 - 23 exp pediatrics/ (0)
 - 24 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (19252)
 - 25 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 - 26 Puberty/ (0)

- 27 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (12647)
- 28 Schools/ (0)
- 29 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
- 30 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (11641)
- 31 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (90)
- 32 or/18-31 (72562)
- 33 17 and 32 (14)
- 34 Economics/ (0)
- 35 exp "Costs and Cost Analysis"/ (0)
- 36 Economics, Dental/ (0)
- 37 exp Economics, Hospital/ (0)
- 38 exp Economics, Medical/ (0)
- 39 Economics, Nursing/ (0)
- 40 Economics, Pharmaceutical/ (0)
- 41 Budgets/ (0)
- 42 exp Models, Economic/ (0)
- 43 Markov Chains/ (0)
- 44 Monte Carlo Method/ (0)
- 45 Decision Trees/ (0)
- 46 econom\$.tw. (6029)
- 47 cba.tw. (69)
- 48 cea.tw. (316)
- 49 cua.tw. (22)
- 50 markov\$.tw. (806)
- 51 (monte adj carlo).tw. (1711)
- 52 (decision adj3 (tree\$ or analys\$)).tw. (370)
- 53 (cost or costs or costing\$ or costly or costed).tw. (12287)
- 54 (price\$ or pricing\$).tw. (916)
- 55 budget\$.tw. (549)

56	expenditure\$.tw. (1158)
57	(value adj3 (money or monetary)).tw. (68)
58	(pharmacoeconomic\$ or (pharmaco adj economic\$)).tw. (57)
59	or/34-58 (20903)
60	"Quality of Life"/ (0)
61	quality of life.tw. (6438)
62	"Value of Life"/ (0)
63	Quality-Adjusted Life Years/ (0)
64	quality adjusted life.tw. (367)
65	(qaly\$ or qald\$ or qale\$ or qtime\$).tw. (325)
66	disability adjusted life.tw. (87)
67	daly\$.tw. (78)
68	Health Status Indicators/ (0)
69	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (426)
70	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (72)
71	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (140)
72	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
73	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)
74	(euroqol or euro qol or eq5d or eq 5d).tw. (336)
75	(qol or hql or hqol or hrqol).tw. (1237)
76	(hye or hyes).tw. (3)
77	health\$ year\$ equivalent\$.tw. (0)
78	utilit\$.tw. (4802)
79	(hui or hui1 or hui2 or hui3).tw. (18)
80	disutili\$.tw. (20)
81	rosser.tw. (0)
82	quality of wellbeing.tw. (1)
83	quality of well-being.tw. (5)

- 84 qwb.tw. (2)
- 85 willingness to pay.tw. (147)
- 86 standard gamble\$.tw. (10)
- 87 time trade off.tw. (33)
- 88 time tradeoff.tw. (7)
- 89 tto.tw. (18)
- 90 or/60-89 (11525)
- 91 59 or 90 (30766)
- 92 33 and 91 (3)
- 93 limit 92 to english language (3)

Database: Embase <1974 to 2019 Week 25>

Search Strategy:

-
- 1 exp kidney failure/ (330779)
 - 2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115064)
 - 3 ((kidney* or renal*) adj1 insufficien*).tw. (29268)
 - 4 ckd*.tw. (44929)
 - 5 ((kidney* or renal*) adj1 fail*).tw. (128105)
 - 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54766)
 - 7 (esrd* or eskd*).tw. (25497)
 - 8 or/1-7 (420393)
 - 9 exp anemia/ (334503)
 - 10 (anemi* or anaemi*).tw. (192311)
 - 11 9 or 10 (370954)
 - 12 8 and 11 (36885)
 - 13 exp hemoglobin/ (309665)
 - 14 hemoglobin blood level/ (61188)
 - 15 exp hemoglobin analysis/ (22911)
 - 16 (haemoglobin* or hemoglobin* or hb or hgb).tw. (246083)
 - 17 or/13-16 (403610)

- 18 12 and 17 (10048)
- 19 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3246394)
- 20 (premat* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1142525)
- 21 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3412794)
- 22 exp pediatrics/ (99771)
- 23 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1532721)
- 24 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (97325)
- 25 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (612398)
- 26 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (97583)
- 27 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (650597)
- 28 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (6711)
- 29 or/19-28 (6066382)
- 30 18 and 29 (2086)
- 31 exp Health Economics/ (800604)
- 32 exp "Health Care Cost"/ (277246)
- 33 exp Pharmacoeconomics/ (194127)
- 34 Monte Carlo Method/ (36365)
- 35 Decision Tree/ (11142)
- 36 econom\$.tw. (335016)
- 37 cba.tw. (12306)
- 38 cea.tw. (32436)
- 39 cua.tw. (1365)
- 40 markov\$.tw. (27240)
- 41 (monte adj carlo).tw. (43448)
- 42 (decision adj3 (tree\$ or analys\$)).tw. (20659)
- 43 (cost or costs or costing\$ or costly or costed).tw. (699771)

- 44 (price\$ or pricing\$).tw. (52416)
- 45 budget\$.tw. (35624)
- 46 expenditure\$.tw. (69197)
- 47 (value adj3 (money or monetary)).tw. (3181)
- 48 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw. (8236)
- 49 or/31-48 (1623511)
- 50 "Quality of Life"/ (428785)
- 51 Quality Adjusted Life Year/ (23848)
- 52 Quality of Life Index/ (2625)
- 53 Short Form 36/ (25941)
- 54 Health Status/ (120207)
- 55 quality of life.tw. (394798)
- 56 quality adjusted life.tw. (17500)
- 57 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (17910)
- 58 disability adjusted life.tw. (3546)
- 59 daly\$.tw. (3516)
- 60 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (38697)
- 61 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2167)
- 62 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8589)
- 63 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (54)
- 64 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (427)
- 65 (euroqol or euro qol or eq5d or eq 5d).tw. (17859)
- 66 (qol or hql or hqol or hrqol).tw. (86455)
- 67 (hye or hyes).tw. (126)
- 68 health\$ year\$ equivalent\$.tw. (40)
- 69 utilit\$.tw. (262792)
- 70 (hui or hui1 or hui2 or hui3).tw. (2082)
- 71 disutili\$.tw. (829)

- 72 rosser.tw. (118)
- 73 quality of wellbeing.tw. (38)
- 74 quality of well-being.tw. (470)
- 75 qwb.tw. (237)
- 76 willingness to pay.tw. (7588)
- 77 standard gamble\$.tw. (1054)
- 78 time trade off.tw. (1607)
- 79 time tradeoff.tw. (279)
- 80 tto.tw. (1528)
- 81 or/50-80 (901702)
- 82 49 or 81 (2382084)
- 83 30 and 82 (241)
- 84 limit 83 to english language (226)
- 85 limit 84 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (83)
- 86 84 not 85 (143)

Database: Econlit <1886 to June 13, 2019>

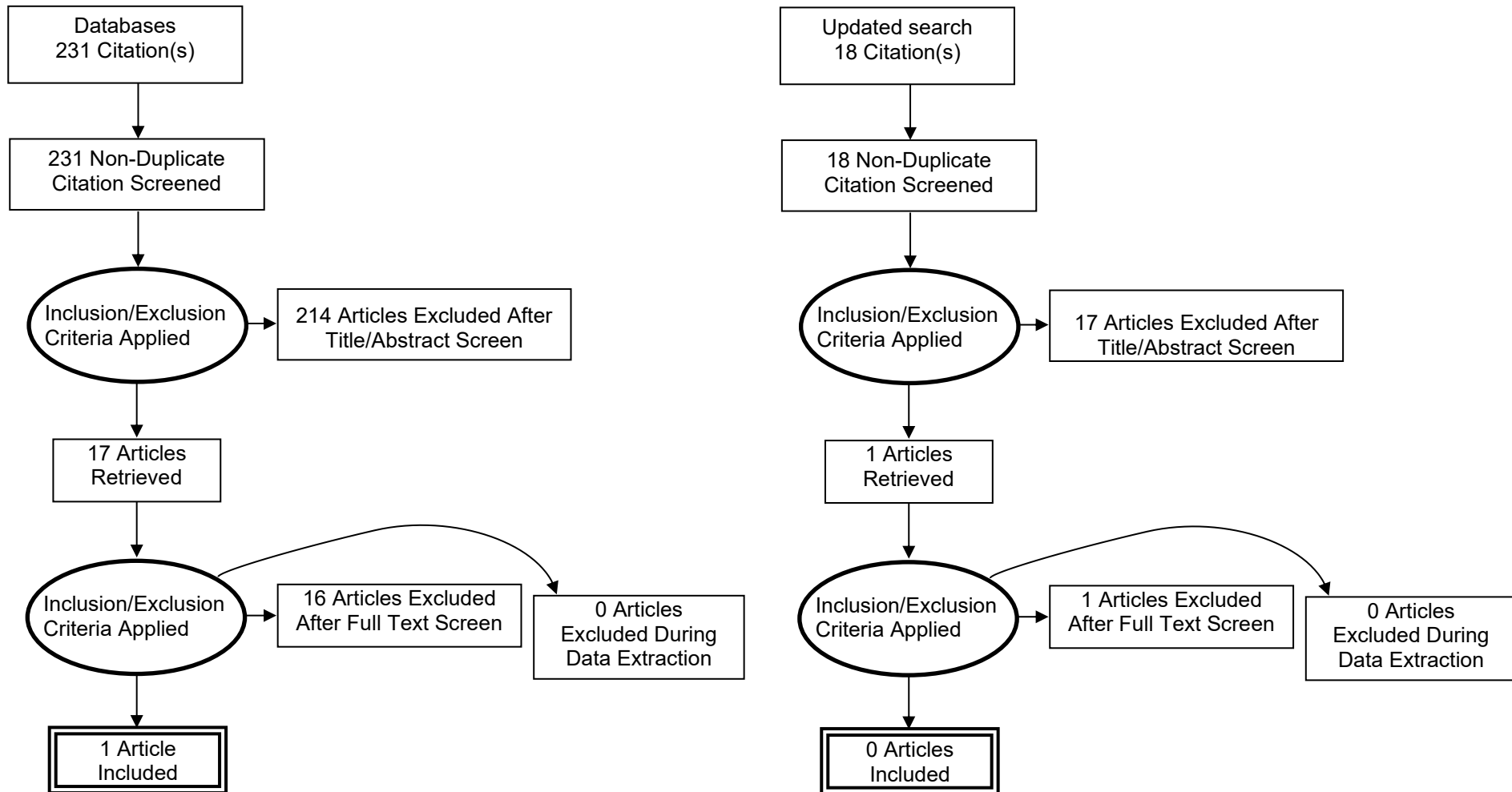
Search Strategy:

-
- 1 [exp Renal Insufficiency, Chronic/] (0)
- 2 ((chronic* or progressi*) adj1 (renal* or kidney*).tw. (20)
- 3 ((kidney* or renal*) adj1 insufficien*).tw. (3)
- 4 ckd*.tw. (4)
- 5 ((kidney* or renal*) adj1 fail*).tw. (32)
- 6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*).tw. (53)
- 7 (esrd* or eskd*).tw. (30)
- 8 ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)
- 9 or/1-8 (97)
- 10 [exp Anemia/] (0)
- 11 (anemi* or anaemi*).tw. (186)

12	10 or 11 (186)		
13	9 and 12 (9)		
14	[exp Hemoglobins/] (0)		
15	(haemoglobin* or hemoglobin* or hb or hgb).tw. (100)		
16	14 or 15 (100)		
17	13 and 16 (2)		
18	[exp Infant/ or Infant Health/ or Infant Welfare/] (0)		
19	(prematu* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (5393)		
20	[exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/] (0)		
21	[Minors/] (0)		
22	(child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (45228)		
23	[exp pediatrics/] (0)		
24	(pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (168)		
25	[Adolescent/ or Adolescent Behavior/ or Adolescent Health/] (0)		
26	[Puberty/] (0)		
27	(adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (8806)		
28	[Schools/] (0)		
29	[Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/] (0)		
30	(pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (47576)		
31	("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (56)		
32	or/18-31 (91050)		
33	17 and 32 (0)		
CRD databases			
1	MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES	538	
	Delete		
2	((chronic* or progressi*) near1 (renal* or kidney*))	489	Delete

3	((kidney* or renal*) near1 insufficien*)	320	Delete
4	(ckd*) 93		Delete
5	((kidney* or renal*) near1 fail*) 836		Delete
6	((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))	354	Delete
7	(esrd* or eskd*)	150	Delete
8	MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder	0	Delete
9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	1407	Delete
10		380	Delete
11	(anemi* or anaemi*)	731	Delete
12	(#10 or #11)	791	Delete
13	MeSH DESCRIPTOR Hemoglobins EXPLODE ALL TREES	493	Delete
14	(haemoglobin* or hemoglobin* or hb or hgb)	1350	Delete
15	(#13 or #14)	1353	Delete
16	#9 AND #12 AND #15	56	Delete
17	(#16) IN NHSEED	19	Delete
18	(#16) IN HTA	5	Delete

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence tables

Morris, 1993

Bibliographic Reference Morris, K P; Skinner, J R; Hunter, S; Coulthard, M G; Short term correction of anaemia with recombinant human erythropoietin and reduction of cardiac output in end stage renal failure.; Archives of disease in childhood; 1993; vol. 68 (no. 5); 644-8

Study details

Study location	UK
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	Overall 48 weeks Crossover at 24 weeks
Sources of funding	Mannhein UK supplied erythropoietin for the study
Inclusion criteria	Children with end stage renal failure and anaemia
Exclusion criteria	Not specified
Sample size	11 children
Condition specific characteristics	End stage renal failure Children included in study had end stage renal failure and anaemia. 5/11 were being treated for hypertension.
Interventions	High Hb target (rHuEPO) r-HuEPO was administered subcutaneously twice weekly by the child or parent at home. The volume of all injections was fixed at 0.5ml. r-HuEPO was commenced at 50 U/kg/week and increased in stepwise increments to a maximum of 400 U/kg/week by week 12, thereafter adjusted to maintain a target haemoglobin concentration of 105-120 g/l Low Hb target (Placebo) Placebo was administered subcutaneously twice weekly by the child or parent at home. The baseline median haemoglobin concentration was 73g/l (range 42-81).
Outcome measures	Left ventricular mass index (g/m ²)

Study arms**High Hb target (r-HuEPO) (N = 6)****Target haemoglobin concentration of 105-120 g/l****Split between study groups****6 children**

Loss to follow-up

7/11 children completed both limbs of the study and included in the analysis. 3 out of the 4 children underwent renal transplantation during the study (unclear which arm) and 1 child died but this was related to his primary disease (in placebo- rHuEPO group)
No. of children included in analysis: 4

% Female

33%

Mean age (SD)

Mean age: 6 years (calculated)

Condition specific characteristics

End stage renal failure
Children were diagnosed with familial haemolytic uraemic syndrome (1/6), dysplasia (2/6), congenital nephrotic syndrome (1/6), posterior urethral valves (1/6) and 1 unknown diagnosis. Mode of dialysis: Peritoneal rapid overnight dialysis- 5/6 Haemodialysis: 1/6

Low Hb target (Placebo) (N = 5)**Maintain Hb at <100 g/l**

Loss to follow-up

7/11 children completed both limbs of the study and included in the analysis. 3 out of the 4 children underwent renal transplantation during the study (unclear which arm) and 1 child died but this was related to his primary disease (in placebo- rHuEPO group)
No. of children included in analysis: 3

% Female

0%

Mean age (SD)

Mean age: 7.78 years (calculated)

Interventions

Low Hb target (Placebo)
Children were diagnosed with focal segmental glomerulosclerosis (1/5), dysplasia (1/5), reflux associated dysplasia (1/5), posterior urethral valves (1/5) and infantile polycystic kidney disease (1/5) Mode of dialysis: Peritoneal rapid overnight dialysis- 4/5 Unknown: 1/5

Cochrane risk of bias tool 2

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

High

(Insufficient information random sequence generation and allocation concealment. Baseline imbalances also present.)

Cochrane risk of bias tool 2

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

(Insufficient information provided on washout period.)

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(Insufficient information random sequence generation and allocation concealment. Baseline imbalances also present. Insufficient information provided on washout period.)

Overall Directness

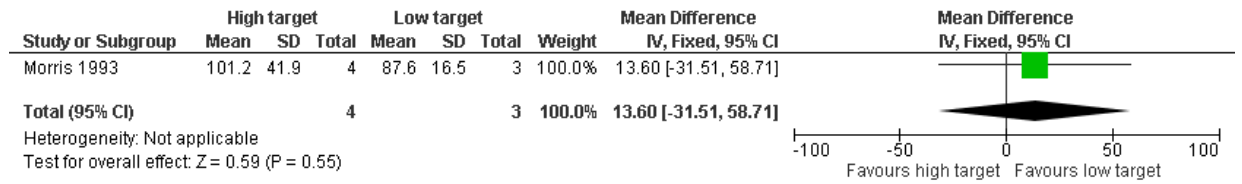
Partially applicable

(Surrogate outcome.)

Appendix F – Forest plots

High target (rHuEPO) vs low target (placebo) [Final values]

Outcome: Left ventricular mass index (MD < 0 favours high Hb target)



Appendix G – GRADE tables

High target (rHuEPO) vs low target (placebo)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD*	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Left ventricular mass index (MD < 0 favours high Hb target based on final values)											
1 Morris 1993	RCT	11 children	MD 13.60 (- 31.51, 58.71)	-	-	8.25	Very serious ¹	N/A ²	Serious ³	Very serious ⁴	Very low
<ol style="list-style-type: none"> 1. Downgrade 2 levels for serious risk of bias due to insufficient information on random sequence generation and allocation concealment Baseline imbalances also present. Insufficient information provided on washout period 2. Inconsistency not applicable 3. Downgrade 1 level for serious indirectness as outcome was not included in review protocol. Outcome is a surrogate measure of left ventricular hypertrophy and a predictor of cardiac morbidity and mortality in adults with hypertension. 4. 95% confidence interval crosses both ends of a defined MID interval. Downgrade 2 levels for very serious imprecision. <p>* Calculated using the SD of the control group for individual studies</p>											

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

None – no economic evaluations relevant to the review question were found.

Appendix J – Health economic model

This review was not prioritised for economic modelling.

Appendix K – Excluded studies

Effectiveness studies

Study	Reason for exclusion
Akhtar N.; Tahir M.; Kiran S. (2010) Recombinant human erythropoietin therapy in predialysis patients of chronic kidney disease. <i>Nephrology Reviews</i> 2(1): 43-46	- Not a relevant study design [Before and after study.]
Brandt, J R, Avner, E D, Hickman, R O et al. (1999) Safety and efficacy of erythropoietin in children with chronic renal failure.. <i>Pediatric nephrology (Berlin, Germany)</i> 13(2): 143-7	- Does not meet objectives of this review [Unclear Hb target ranges.]
Clement F M, Klarenbach S, Tonelli M, Johnson J A, Manns B J (2009) The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. <i>Archives of Internal Medicine</i> 169(12): 1104-1112	- Does not include population of interest [Excluded studies which included population aged under 18]
Cody J.D. and Hodson E.M. (2016) Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis. <i>Cochrane Database of Systematic Reviews</i> 2016(3): cd003266	- Does not include population of interest [Did not include studies which included children and young people]
Cody June D, Daly Conal, Campbell Marion K, Khan Izhar, Rabindranath Kannaiyan S, Vale Luke, Wallace Sheila A, MacLeod Alison M, Grant Adrian M, Pennington Susan, Nistor Ionut, Bolignano Davide, Webster Angela C (2005) Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. <i>Cochrane Database of Systematic Reviews: Reviews issue3</i>	- More recent systematic review included that covers the same topic
Ghobrial, EE, Salama, KM, Shiba, MF et al. (2013) The effect of anemia management on chronic renal failure progression. <i>Egyptian pediatric association gazette</i> 61(1): 37-41	- Does not report outcomes of interest.
Guedes, M., Guetter, C.R., Ermano, L.H.O. et al. (2020) Physical health-related quality of life at higher achieved hemoglobin levels among chronic kidney disease patients: a systematic review and meta-analysis. <i>BMC Nephrology</i> 21(1): 259	- Does not include population of interest [Adults]
Jing Z, Wei-jie Y, Nan Z, Yi Z, Ling W (2012) Hemoglobin targets for chronic kidney disease patients with anemia: a systematic review and meta-analysis. <i>PLOS ONE</i> 7(8)	- Does not include population of interest [Systematic review only included studies which included adults.]
Macdougall, Iain C; Temple, R Mark; Kwan, Jonathan T C (2007) Is early treatment of anaemia with epoetin-alpha beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial.. <i>Nephrology, dialysis, transplantation : official publication of the European Dialysis and</i>	- Does not include population of interest [Included population aged 18 years to 85 years.] - Comparator in study does not match that specified in protocol [Patients were not assigned to different doses of EPO.]

Study	Reason for exclusion
Transplant Association - European Renal Association 22(3): 784-93	
Morris, K P, Sharp, J, Watson, S et al. (1993) Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia.. Archives of disease in childhood 69(5): 580-6	- Data not reported in an extractable format
Palmer S.C., Navaneethan S.D., Craig J.C. et al. (2010) Meta-analysis: Erythropoiesis-stimulating agents in patients with chronic kidney disease. Annals of Internal Medicine 153(1): 23-33	- Systematic review used as source of primary studies
Phrommintikul A, Haas S J, Elsik M, Krum H (2007) Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 369: 381-388	- Does not include population of interest [Did not include studies which included children and young people]
Rossert, Jerome, Levin, Adeera, Roger, Simon D et al. (2006) Effect of early correction of anemia on the progression of CKD.. American journal of kidney diseases : the official journal of the National Kidney Foundation 47(5): 738-50	- Does not include population of interest [Included population aged 18 years to 75 years.]
Strippoli, G F M; Navaneethan, S D; Craig, J C (2006) Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease.. The Cochrane database of systematic reviews: cd003967	- Systematic review used as source of primary studies
Strippoli, G F, Manno, C, Schena, F P et al. (2003) Haemoglobin and haematocrit targets for the anaemia of chronic renal disease.. The Cochrane database of systematic reviews: cd003967	- More recent systematic review included that covers the same topic
Strippoli, Giovanni F M, Craig, Jonathan C, Manno, Carlo et al. (2004) Hemoglobin targets for the anemia of chronic kidney disease: a meta-analysis of randomized, controlled trials.. Journal of the American Society of Nephrology : JASN 15(12): 3154-65	- Systematic review used as source of primary studies
Ye, Yuqiu, Liu, Hongyong, Chen, Yanbing et al. (2018) Hemoglobin targets for the anemia in patients with dialysis-dependent chronic kidney disease: a meta-analysis of randomized, controlled trials.. Renal failure 40(1): 671-679	- Does not include population of interest [Systematic review excluded studies which included population aged <18 years.]
Ye, Yuqiu, Liu, Hongyong, Chen, Yanbing et al. (2018) Hemoglobin targets for the anemia in patients with dialysis-dependent chronic kidney disease: a meta-analysis of randomized, controlled trials.. Renal failure 40(1): 671-679	- Does not include population of interest [Systematic review excluded studies which included population aged <18 years.]

Economic studies

Study	Reason
Clement FM, Klarenbach S, Tonelli M, Wiebe N, Hemmelgarn B, Manns BJ (2010) An economic evaluation of erythropoiesis-stimulating agents in CKD. American Journal of Kidney Diseases 56(6): 1050-1061	- Does not include population of interest [adult population aged ≥ 16 years]

Study	Reason
Glenngard A H, Persson U, Schon S (2008) Cost-effectiveness analysis of treatment with epoietin-alpha for patients with anaemia due to renal failure: the case of Sweden. <i>Scandinavian Journal of Urology and Nephrology</i> 42(1): 66-73	- Does not include population of interest [adult population]
Nguyen, Timothy V and Goldfarb, David S (2011) Implications of a reduction in the hemoglobin target in erythropoiesis-stimulating agent-treated hemodialysis patients. <i>Nephron extra</i> 1(1): 212-6	- Not an economic evaluation
Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B, Manns B (2008) Erythropoiesis-stimulating agents for anemia of chronic kidney disease: systematic review and economic evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH): 59	- Does not include population of interest [adult population]
Tonelli M., Winkelmayr W.C., Jindal K.K. et al. (2003) The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. <i>Kidney International</i> 64(1): 295-304	- Does not include population of interest [population age not specified]

Appendix L – Research recommendations– full details

L.1.1 Research recommendation

What is the efficacy and safety of different aspirational Hb targets for children and young people with CKD undergoing treatment for anaemia?

L.1.2 Why this is important

One small crossover RCT of very low quality was identified which compared high haemoglobin (Hb) target with low Hb target. However, due to the lack of evidence the committee were unable to make new recommendations for children and young people. The committee also identified that in practice, higher Hb targets than those suggested in the current recommendations, are being maintained in children and young people. Based on this knowledge and the lack of evidence in the population group, the committee identified this as an important area for research to inform future updates.

L.1.3 Rationale for research recommendation

Importance to patients	It is uncertain what the optimal Hb target for children and young people is. There is also some uncertainty about safe levels of Hb in children and young people.
Relevance to NICE guidance	Further research would enable a committee to give more clarity in the recommendations.
Relevance to the NHS	The committee was aware that children and young people are routinely being maintained on a higher level than is currently recommended so this would deal with uncertainty in practice and disparity between practice and NICE guideline recommendations.
National priorities	None
Current evidence base	One crossover RCT of very low quality
Equality considerations	None identified.

L.1.4 Modified PICO table

Population	Children and young people with CKD undergoing treatment for anaemia
Intervention	Different haemoglobin (Hb) target levels
Comparator	Standard Hb targets
Outcome	<ul style="list-style-type: none"> • Efficacy (e.g. change in haemoglobin levels) • Adverse events (e.g. cardiovascular events, infections mortality and access site thrombosis) • Quality of life
Study design	Parallel randomised controlled trial
Timeframe	Long term

FINAL

Aspirational haemoglobin target range for children and young people with CKD

Additional information

None
