

Guideline Summary NGC-10726

Guideline Title

Anaemia management in people with chronic kidney disease.

Bibliographic Source(s)

National Clinical Guideline Centre. Anaemia management in people with chronic kidney disease. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun 3. 43 p. (NICE guideline; no. 8).

Guideline Status


This is the current release of the guideline.

This guideline updates a previous version: National Clinical Guideline Centre. Anaemia management in people with chronic kidney disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Feb. 38 p. (Clinical guideline; no. 114).

This guideline meets NGC's 2013 (revised) inclusion criteria.

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- **March 31, 2015 – Feraheme (ferumoxytol)** : The U.S. Food and Drug Administration (FDA) is strengthening an existing warning that serious, potentially fatal allergic reactions can occur with the anemia drug Feraheme (ferumoxytol). FDA changed the prescribing instructions and approved a Boxed Warning, FDA's strongest type of warning, regarding these serious risks. Also added is a new Contraindication, a strong recommendation against use of Feraheme in patients who have had an allergic reaction to any intravenous (IV) iron replacement product.

Scope

Disease/Condition(s)

Anaemia of chronic kidney disease (CKD)

Guideline Category

Diagnosis
Evaluation
Management
Treatment

Clinical Specialty

Family Practice
Geriatrics
Hematology
Internal Medicine
Nephrology
Pediatrics

Intended Users

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Public Health Departments

Guideline Objective(s)

To address the appropriate management of anaemia of chronic kidney disease (CKD) for patients in the National Health Service (NHS)

Target Population

Adults, children, and young people with a clinical diagnosis of anaemia associated with chronic kidney disease (CKD) including those:

- With pre-dialysis CKD
- With established renal failure receiving conservative management
- With established renal failure receiving renal replacement therapy
- Who have had renal transplant surgery

Note: Groups that are not covered by the guideline include people with anaemia not principally caused by CKD, for example, anaemia caused by haematological disease (including sickle cell disease), acute and chronic inflammatory disease states, malignancy (myeloma as a cause of CKD and anaemia will be included), acquired immunodeficiency syndrome, acute kidney injury.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Investigation of haemoglobin (Hb) levels
2. Investigation of estimated glomerular filtration rate (eGFR)
3. Tests to determine iron status and predict response to therapy
 - Percentage of hypochromic red blood cells (% HRC)
 - Reticulocyte Hb content (CHR) or equivalent test
 - Combination of transferrin saturation and serum ferritin measurement

Management/Treatment

1. Erythropoiesis-stimulating agents (ESAs), including consideration of:
 - Patient preference
 - Route of administration
 - Dose and frequency
 - Adjusting ESA therapy
 - Optimal Hb levels (determining individual aspirational Hb ranges)
2. Iron supplements (oral and intravenous)
3. Treatment of clinically relevant hyperparathyroidism
4. Blood transfusion when transplant isn't an option
5. Maintenance of stable Hb levels
6. Monitoring of iron status and Hb levels
7. Detecting ESA resistance
8. Managing ESA resistance
9. Use of patient-centred care, including
 - Provision of information to patient and general practitioner (GP)
 - Protocols defining roles and responsibilities of healthcare professionals in primary and secondary care
 - Consideration of patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA, and storage
 - Provision of culturally and age-appropriate patient education programmes

Note: The following were considered but not recommended: measurement of erythropoietin levels; supplements of vitamin C, folic acid or carnitine; and androgens.

Major Outcomes Considered

- Diagnostic accuracy of tests for predicting response to iron therapy
 - Sensitivity
 - Specificity
 - Positive and negative predictive values
- Iron deficiency treatment
 - Epoetin dose
 - Efficacy or haemoglobin (Hb) response
 - Compliance
 - Patient preference
 - Side effects
 - Safety (adverse events)
 - Quality of life
- Erythropoiesis-stimulating agent (ESA) resistance
 - Hb levels
 - Morbidity
 - Hospitalisation
 - Mortality
- Management of anaemia of chronic kidney disease (CKD) and an acute infectious illness
 - Hb levels
 - Blood transfusion

- ESA use
- Morbidity
- Mortality
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). Full details regarding the 2006, 2011, and 2015 guideline methodology can be found in the full version of the guideline (see the "Availability of Companion Documents" field).

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the National Clinical Guideline Centre technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full guideline appendices [see the "Availability of Companion Documents" field]). A total of five review questions were identified as part of this update.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within The guidelines manual (2012) (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, EMBASE, and The Cochrane Library. All searches were updated on August 14, 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G in the full guideline appendices.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearinghouse (NGC) (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- National Health Service (NHS) Evidence Search (www.evidence.nhs.uk).

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to anaemia and chronic kidney disease (CKD) in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE using a specific economic filter, from 2011, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix F in the full guideline appendices. All searches were updated on August 14, 2014. Papers were not considered if published after that date.

Evidence of Effectiveness

Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C in the full guideline appendices [see the "Availability of Companion Documents" field]).

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C in the full guideline appendices. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix M in full guideline appendices. The GDG was consulted about any uncertainty about inclusion or exclusion.

The guideline population was defined to be people with anaemia of CKD. For some review questions, the review population was defined as people who were suspected of or were under investigation for anaemia of CKD.

Randomised trials, non-randomised trials, and observational studies (including diagnostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected net health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement

across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The guidelines manual [2012]) and the health economics review protocol in Appendix D in the full guideline appendices).

Number of Source Documents

Refer to Appendix E in the full guideline appendices (see the "Availability of Companion Documents" field), Clinical article selection, for a flow chart detailing the number of records identified in searching, the number of studies included and excluded, and the reasons for exclusion for each review question in the 2015 update. Refer to Appendix F in the full guideline appendices for details on economic article selection for all questions in the 2015 update.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Quality Element	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). Full details regarding the 2006, 2011, and 2015 methodology can be found in the full version of the guideline (see the "Availability of Companion Documents" field).

Evidence of Effectiveness

Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C in the full guideline appendices [see the "Availability of Companion Documents" field]).

Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual (2012). For diagnostic questions, the QUADAS-2 checklist was followed (see Appendix F of The guidelines manual [2012] [see the "Availability of Companion Documents" field]).

Key information was extracted on the study's methods, PICO (patient, intervention, comparison and outcome) factors and results. These were presented in summary tables (in each review chapter of the full version of the guideline) and evidence tables (in Appendix H in the full guideline appendices).

Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Guideline Development Group (GDG) meetings.

- Randomised studies: data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development, and Evaluation (GRADE) profiles (for intervention reviews).
- Observational studies: data were presented as a range of values in GRADE profiles.
- Diagnostic studies: A diagnostic meta-analysis was conducted for two tests, (transferrin saturation [TSAT], less than 20% and serum ferritin [SF], less than 100 micrograms/litre), as data was available from five or more studies at a particular threshold. For the remainder of the tests, data were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in receiver operating curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively (given data were reported at the same thresholds).

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as the percentage of patients achieving target haemoglobin (Hb) levels, and the number of patients needing to begin erythropoiesis-stimulating agent (ESA) therapy or receive one or more blood transfusions.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as mean change of Hb from baseline were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics, and 95% confidence interval (CI) or

standard error (SE); this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the SE for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Therefore, aspects of quality assessment, such as imprecision of effect, could not be assessed for evidence of this type.

Where reported, time-to-event data was presented as a hazard ratio.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect on these subpopulations. For example, it was agreed that evidence for the review on iron therapies prior to and on ESA therapy would include data that will be stratified by renal replacement therapy into patients on haemodialysis, and pre-dialysis patients and patients on all other renal replacement therapy (peritoneal dialysis). It was agreed that data would not be stratified by stage of chronic kidney disease (CKD).

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present (and data was not stratified), the GDG carried out predefined subgroup analyses for patients on haemodialysis, and pre-dialysis patients and patients on all other renal replacement therapy (peritoneal dialysis). Sensitivity analysis based on the quality of studies was also carried out, eliminating studies at overall high risk of bias (randomisation, allocation concealment and blinding, missing outcome data).

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity, then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the SE was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and SE using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value is reported as ' $p \leq 0.001$ ', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available, then the methods described in Section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences (ARDs) were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Network Meta-Analysis

A network meta-analysis (NMA) was planned for the review questions on iron therapy prior to and on ESA therapy. This type of analysis would have simultaneously compared multiple treatments in a single meta-analysis, preserving the randomisation of randomised controlled trials (RCTs) included in the reviews of direct comparisons trials. Due to a lack of data, the NMA could not be undertaken.

Data Synthesis for Diagnostic Meta-Analysis and Test Accuracy Reviews

Data and Outcomes:

For the reviews of diagnostic test accuracy, a positive result on the index test was found if the patient had values of the measured quantity above a threshold value, and different thresholds could be used. Diagnostic test accuracy measures used in the analysis included area under the receiver operating characteristics (ROC) curve, and, for different thresholds, sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition, for example, those who are iron deficient and those who are not iron deficient, and, in practice, it varies amongst studies. For the diagnostic meta-analysis, sensitivity was considered to be more important than specificity. A high sensitivity (true positives) of a test can pick up the majority of the correct cases with iron deficiency and who are responsive to iron therapy; conversely, a high specificity (true negatives) can correctly exclude people without iron deficiency and so are unresponsive to iron therapy.

Data Synthesis:

Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5. In order to do this, 2x2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else, were derived from raw data or calculated from the set of test accuracy statistics (calculated 2x2 tables can be found in Appendix O in the full guideline appendices).

To allow a comparison between tests, summary ROC curves were generated for each diagnostic test from the pairs of sensitivity and specificity calculated from the 2x2 tables, selecting 1 threshold per study. A ROC plot shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). Data were entered into RevMan5 and ROC curves were fitted using the Moses Littenburg approach. In order to compare diagnostic tests, 2 or more tests were plotted on the same graph. The performance of the different diagnostic tests was then assessed by examining the summary ROC curves visually: the test that had a curve lying closest to the upper left corner (100% sensitivity and 100% specificity) was interpreted as the best test.

A second analysis was conducted by restricting the set of studies to those with the same clinically relevant threshold as agreed by the GDG, to ensure the data were comparable. They were presented as forest plots and ROC curves, and heterogeneity was investigated.

Area under the ROC curve (AUC) data for each study were also plotted on a graph for each diagnostic test. The AUC describes the overall diagnostic accuracy across the full range of thresholds.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots where appropriate (only when there were similar thresholds).

When data from 5 or more studies were available for one test at a clinically relevant threshold, a diagnostic meta-analysis was carried out. A diagnostic meta-analysis was conducted for two tests (TSAT, less than 20% and SF, less than 100 micrograms/litre) as data was available from five or more studies at a particular threshold. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one ROC curve in Microsoft EXCEL software (for forest plots please see Appendix L in the full guideline appendices). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (in WinBUGS® software - for the program code see Appendix P in the full guideline appendices). This model also assesses the variability by incorporating the precision by which sensitivity and specificity have been measured in each study. A confidence ellipse is shown in the graph that indicates the confidence region around the summary sensitivity and specificity point. A summary ROC curve is also presented. From the WinBUGS® output, the GDG reports the summary estimate of sensitivity and specificity (plus their 95% CIs) as well as between study variation measured as logit sensitivity and specificity as well as correlations between the two measures of variation. The summary diagnostic odds ratio with its 95% CI is also reported.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org>). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment, while the 'Clinical evidence summary of findings' table includes pooled outcome data, and where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation, or median and range) for continuous outcomes and frequency of events (n/N; the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 15 in the full version of the guideline. Each element was graded using the quality levels listed in Table 16 of the full version of the guideline. The main criteria considered in the rating of these elements are discussed in Section 2.18.5 in the full version of the guideline). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component

were summed to obtain an overall assessment for each outcome (see the "Rating Scheme for the Strength of the Evidence" field).

The GRADE toolbox is currently designed only for randomised trials and observational studies, but the GDG adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Grading the Quality of Clinical Evidence

The overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points, respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted, respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the Sections 2.18.6 to 2.18.9 of the full version of the guideline.

Assessing Clinical Importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared with the comparison group, then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome
- A brief description of the participants
- An indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- A description of the overall quality of evidence (GRADE overall quality)

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected net health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual (2012) (see the "Availability of Companion Documents" field)
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I in the full guideline appendices)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter of the full version of the guideline for each review question)

When no relevant economic studies were found from the economic literature review, relevant UK National Health Service (NHS) unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual (2012). It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 19 in the full version of the guideline for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). Full details regarding the 2006, 2011, and 2015 methodology can be found in the full version of the guideline (see the "Availability of Companion Documents" field).

Developing Recommendations

Over the course of the guideline development process, the Guideline Development Group (GDG) was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I in the full guideline appendices (see the "Availability of Companion Documents" field).
- Summaries of clinical and economic evidence and quality (as presented in Chapters 4, 6 and 7 in the full version of the guideline).
- Forest plots and summary ROC curves (see Appendix L in the full guideline appendices).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline update (see Appendix O in the full guideline appendices).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, and recommendations made in other relevant guidelines, patient preferences and equality issues. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effects and others are not. In these circumstances, the recommendation is generally weaker, although, it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter in the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer...') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation Wording in Guideline Updates

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2006]. In particular, for recommendations labelled [2006] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the Guideline Development Group (GDG) after formation of the review questions and consideration of the available health economic evidence.

The GDG identified a comparison of intravenous iron therapy regimens and strategies for determining which patients will respond to iron therapy as the highest priority areas for original economic modelling. This was because iron therapy represents a substantial cost both in terms of drug acquisition, staff time and other on-costs; these costs vary considerably by regimen. There are significant differences in testing protocols used and these can result in patients receiving iron unnecessarily. The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the National Clinical Guideline Centre.

Full methods for the cost-effectiveness analysis comparing different strategies for determining which patients will respond to iron therapy are described in Appendix O in the full guideline appendices.

For the comparison of iron therapy regimens, cost-effectiveness analysis was not feasible mainly for the following reasons:

- The clinical data was found to be low quality, sparse and inconclusive
- The list prices of intravenous iron regimens are not reflective of the typical prices faced by Trusts (which are commercial in confidence)
- The list prices of erythropoiesis-stimulating agent (ESA) therapy regimens are not reflective of the typical prices faced by Trusts (which are commercial in confidence)

Therefore, the GDG conducted a cost analysis based on list prices, which included staff-time, clinic space, transport and disposables for two subgroups:

- a. Haemodialysis and
- b. Pre-dialysis and peritoneal dialysis

On the basis of this analysis, the GDG developed a simple costing tool for Trusts to enter their own prices and determine the lowest cost regimen locally.

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per QALY gained compared with the next best strategy

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues about the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

In the Absence of Economic Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service (NHS) unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication, but we have no reason to believe they have changed substantially.

See Appendix O: Cost-effectiveness analysis for the 2015 update: Diagnostic tests for predicting response to iron therapy of the 2015 full version of the guideline.

See also the following in the Appendices from 2006 and 2011 (see the "Availability of Companion Documents" field):

- Appendix W: Cost-effectiveness analysis of optimal treatment target for the 2011 rapid update
- Appendix X: Health economic calculation: route of administration of ESAs

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Validation Process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE Web site.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation), and are defined at the end of the "Major Recommendations" field.

Recommendations are marked as **[new 2015]**, **[2011]**, **[2006]**, **[2011, amended 2015]** or **[2006, amended 2015]**:

- **[new 2015]** indicates that the evidence has been reviewed and the recommendation has been added or updated.
- **[2011]** indicates that the evidence has not been reviewed since 2011.
- **[2006]** indicates that the evidence has not been reviewed since 2006.
- **[2006, amended 2015]** indicates that the evidence has not been reviewed since 2006, but changes have been made to the recommendation wording that change the meaning.
- **[2011, amended 2015]** indicates that the evidence has not been reviewed since 2011, but changes have been made to the recommendation wording that change the meaning.

Diagnostic Evaluation and Assessment of Anaemia

Diagnostic Role of Haemoglobin (Hb) Levels

Consider investigating and managing anaemia in people with chronic kidney disease (CKD) if:

- Their Hb level falls to 110 g/litre or less (or 105 g/litre or less if younger than 2 years) **or**
- They develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy, and palpitations) **[2011]**

Diagnostic Role of Glomerular Filtration Rate

An estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m² should trigger investigation into whether anaemia is due to CKD. When the eGFR is greater than or equal to 60 ml/min/1.73m² the anaemia is more likely to be related to other causes. **[2006]**

Diagnostic Tests to Determine Iron Status and Predict Response to Iron Therapy

Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months (every 1 to 3 months for

people receiving haemodialysis).

- Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.
- If using % HRC is not possible, use reticulocyte Hb content (CHR; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.
- If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100micrograms/litre). **[new 2015]**

Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. **[new 2015]**

Measuring Erythropoietin

Do not routinely consider measurement of erythropoietin levels for the diagnosis or management of anaemia in people with anaemia of CKD. **[2006]**

Managing Anaemia

Initiation of Erythropoiesis-Stimulating Agent (ESA) Therapy in Iron-Deficient Patients

ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. **[2006]**

Maximum Iron Levels in People with Anaemia of CKD

In people treated with iron, serum ferritin levels should not rise above 800 micrograms/litre. In order to prevent this, the dose of iron should be reviewed when serum ferritin levels reach 500 micrograms/litre. **[2006]**

Clinical Utility of ESA Therapy in Iron-Replete Patients

The pros and cons of a trial of anaemia management should be discussed between the clinician, the person with anaemia of CKD, and their families and carers if applicable. **[2006]**

ESAs need not be administered where the presence of comorbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. **[2006]**

Initiate a trial of anaemia correction when there is uncertainty over whether the presence of comorbidities, or the prognosis, would negate benefit from correcting the anaemia with ESAs. **[2006]**

Where a trial of ESA therapy has been performed, assess the effectiveness of the trial after an agreed interval. Where appropriate, a mutual decision should be agreed between the clinician, the person with anaemia of CKD and their families and carers on whether or not to continue ESA therapy. **[2006]**

Review all people started on ESA therapy after an agreed interval in order to decide whether or not to continue using ESAs. **[2006]**

Nutritional Supplements

Supplements of vitamin C, folic acid, or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. **[2006]**

Androgens

In people with anaemia of CKD, androgens should not be used to treat the anaemia. **[2006]**

Hyperparathyroidism

In people with anaemia of CKD, clinically relevant hyperparathyroidism should be treated to improve the management of the anaemia. **[2006]**

Patient-centred Care: ESAs

Give people offered ESA therapy and their general practitioners (GPs) information about why ESA therapy is required, how it works and what benefits and side effects may be experienced. **[2006]**

When managing the treatment of people with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of healthcare professionals in primary and secondary care. **[2006]**

Inform people receiving ESA therapy about the importance of concordance with therapy and the consequences of poor concordance. **[2006]**

When prescribing ESA therapy, healthcare professionals should take into account patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA, and storage. **[2006]**

In order for people to self-administer their ESA in a way that is clinically effective and safe, arrangements should be made to provide ready, reasonable and uninterrupted access to supplies. **[2006]**

Patient Education Programmes

Offer culturally and age-appropriate patient education programmes to all people diagnosed with anaemia of CKD (and their families and carers). These should be repeated as requested, and according to the changing circumstances of the patient. They should include the following key areas:

- Practical information about how anaemia of CKD is managed
- Knowledge (for example, about symptoms, iron management, causes of anaemia, associated medications, phases of treatment)
- Professional support (for example, contact information, community services, continuity of care, monitoring, and feedback on progress of results)
- Lifestyle (for example, diet, physical exercise, maintaining normality, and meeting other patients)
- Adaptation to chronic disease (for example, previous information and expectations, and resolution of symptoms) **[2006]**

Assessment and Optimisation of Erythropoiesis

Benefits of Treatment with ESAs

Offer treatment with ESAs to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. **[2006]**

Blood Transfusions

Avoid blood transfusions where possible in people with anaemia of CKD in whom kidney transplant is a treatment option. **[2006]**

In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, follow the relevant national guidance¹. **[2006, amended 2015]**

Comparison of ESAs

Discuss the choice of ESA with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs. There is no evidence to distinguish between ESAs in terms of efficacy. **[2006]**

Coordinating Care

People with anaemia of CKD should have access to a designated contact person or persons who have principal responsibility for their anaemia management and who have skills in the following activities:

- Monitoring and managing a caseload of patients in line with locally agreed protocols

- Providing information, education and support to empower patients and their families and carers to participate in their care
- Coordinating an anaemia service for people with CKD, working between secondary and primary care and providing a single point of contact, to ensure patients receive a seamless service of the highest standard
- Prescribing medicines related to anaemia management and monitoring their effectiveness **[2006]**

Providing ESAs

ESA therapy should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan that is patient-centred and includes:

- Continuity of drug supply
- Flexibility of where the drug is delivered and administered
- The lifestyle and preferences of the patient
- Cost of drug supply
- Desire for self-care where appropriate
- Regular review of the plan in light of changing needs **[2006]**

ESAs: Optimal Route of Administration

The person with anaemia of CKD and the prescriber should agree (and revise as appropriate) the route of administration of ESAs, taking into account the following factors:

- Patient population (for example, haemodialysis patients)
- Pain of injection
- Frequency of administration
- The lifestyle and preferences of the patient
- Efficacy (for example, subcutaneous versus intravenous administration, or long-acting versus short-acting preparations)
- Cost of drug supply **[2006]**

The prescriber should take into account that when using short-acting ESAs, subcutaneous injection allows the use of lower doses of drugs than intravenous administration. **[2006]**

ESAs: Dose and Frequency

When correcting anaemia of CKD, the dose and frequency of ESA should be:

- Determined by the duration of action and route of administration of the ESA
- Adjusted to keep the rate of Hb increase between 10 and 20 g/litre/month **[2006]**

Optimal Hb Levels

When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:

- Patient preferences
- Symptoms and comorbidities
- The required treatment **[2011]**

The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.

- Typically maintain² the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.
- To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range's limits). **[2011, amended 2015]**

Consider accepting Hb levels below the agreed aspirational range if:

- High doses³ of ESAs are required to achieve the aspirational range **or**
- The aspirational range is not achieved despite escalating ESA doses **[2011]**

Age alone should not be a determinant for treatment of anaemia of CKD. **[2006]**

Adjusting ESA Treatment

Optimise iron status before or coincident with the initiation of ESA administration and during maintenance treatment with ESAs. **[2006, amended 2011]**

Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor antagonists is not precluded, but if they are used, an increase in ESA therapy should be considered. **[2006]**

Take into account Hb measurements when determining the dose and frequency of ESA administration.

- Investigate the cause of an unexpected change in Hb level (that is, intercurrent illness, bleeding) to enable intervention and optimise iron status.
- Increase or decrease ESA dose and/or frequency when Hb measurements fall outside action thresholds (usually below 105 g/litre or above 115 g/litre), or for example when the rate of change of Hb suggests an established trend (for example, greater than 10 g/litre/month). **[2006, amended 2011]**

Treating Iron Deficiency: Correction

Offer people with anaemia of CKD who are receiving ESAs iron therapy to achieve⁴:

- % Hb less than 6% (unless ferritin is greater than 800 micrograms/litre)
- Reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)

If the above tests are not available or the person has thalassaemia or thalassaemia trait, iron therapy should maintain transferrin saturation greater than 20% and serum ferritin level greater than 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Most patients will need 500 to 1000 mg of iron for adults or equivalent doses for children⁵, in a single or divided dose depending on the preparation. Intravenous iron should be administered in a setting with facilities for resuscitation. **[new 2015]**

Treating Iron Deficiency: Maintenance

Once % Hb is less than 6%, reticulocyte Hb count or equivalent tests are above 29 pg, or transferrin saturation is greater than 20% and serum ferritin level is greater than 100 micrograms/litre, offer maintenance iron to people with anaemia of CKD who are receiving ESAs.

The dosing regimen will depend on modality, for example haemodialysis patients will need the equivalent of 50 to 60 mg intravenous iron per week (or an equivalent dose in children⁵ of 1 mg/kg/week). **[new 2015]**

ESAs: Monitoring Iron Status During Treatment

Offer iron therapy to people⁵ receiving ESA maintenance therapy to keep their⁴:

- % HRC less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
- Reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
- Transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre)

The marker of iron status should be monitored every 1 to 3 months in people receiving haemodialysis.

In people who are pre-dialysis⁶ or receiving peritoneal dialysis, levels are typically monitored every 3 months. If these people have a normal full blood count there is little benefit in checking iron status. **[new 2015]**

Iron Therapy for People Who Are Iron Deficient and Not on ESA Therapy

Offer iron therapy to people⁵ with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see "Optimal Hb Levels"), offer intravenous iron therapy.
- For people who are receiving haemodialysis, offer intravenous iron therapy. Offer oral iron therapy to people who are receiving haemodialysis only if:
 - Intravenous iron therapy is contraindicated **or**
 - The person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. **[new 2015]**

Discuss the results of the iron therapy with the person or, where appropriate, with their family or carers and offer ESA therapy if needed (see "Benefits of treatment with ESAs"). **[new 2015]**

Iron Therapy for People Who Are Iron Deficient and Receiving ESA Therapy

Offer iron therapy to people⁵ with anaemia of CKD who are iron deficient and who are receiving ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For adults and young people, offer intravenous iron therapy.
- For children who are receiving haemodialysis, offer intravenous iron therapy.
- For children who are not receiving haemodialysis, consider oral iron. If the child is intolerant of oral iron or target Hb levels are not reached within 3 months (see "Optimal Hb Levels"), offer intravenous iron therapy. **[new 2015]**

Offer oral iron therapy to adults and young people who are receiving ESA therapy only if:

- Intravenous iron therapy is contraindicated **or**
- The person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy **[new 2015]**

When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency⁷ intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:

- Preferences of the person with anaemia of CKD or, where appropriate, their family or carers
- Nursing and administration costs
- Cost of local drug supply
- Provision of resuscitation facilities

Intravenous iron administered at a low dose and high frequency⁸ may be more appropriate for all children⁵ and for adults who are receiving in-centre haemodialysis. **[new 2015]**

Monitoring Treatment of Anaemia of CKD

Monitoring Iron Status

People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The length of time to monitoring of iron status is dependent on the product used and the amount of iron given. **[2006]**

Routine monitoring of iron stores to prevent iron overload using serum ferritin should be at intervals of 1 to 3 months. **[2006, amended 2015]**

Monitoring Hb Levels

In people with anaemia of CKD, monitor Hb:

- Every 2 to 4 weeks in the induction phase of ESA therapy
- Every 1 to 3 months in the maintenance phase of ESA therapy
- More actively after an ESA dose adjustment
- In a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local healthcare systems **[2006]**

Detecting ESA Resistance

After other causes of anaemia, such as intercurrent illness or chronic blood loss, have been excluded, people with anaemia of CKD should be considered resistant to ESAs when:

- An aspirational Hb range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5 micrograms/kg/week of darbepoetin **or**
- There is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range **[2006]**

In people with CKD, pure red cell aplasia (PRCA) is indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. Confirm PRCA by the presence of anti-erythropoietin antibodies together with a lack of pro-erythroid progenitor cells in the bone marrow. **[2006]**

In people with anaemia of CKD, aluminium toxicity should be considered as a potential cause of a reduced response to ESAs after other causes, such as intercurrent illness and chronic blood loss, have been excluded. **[2006]**

Managing ESA Resistance

In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, perform a desferrioxamine test and review patient's management accordingly. **[2006]**

Consider specialist referral for ESA-induced PRCA. **[2006, amended 2011]**

Role of Blood Transfusion in Managing ESA Resistance

Consider referring people with ESA resistance to a haematology service, particularly if an underlying haematological disorder is suspected. **[new 2015]**

Evaluate and discuss the risks and benefits of red cell transfusion with the person or, where appropriate, with their family or carers. **[new 2015]**

Take into account the person's symptoms, quality of life, underlying conditions and the chance of a future successful kidney transplant, in addition to Hb levels, when thinking about the need for red cell transfusion. **[new 2015]**

Review the rate of red cell transfusion and consider a trial period of stopping ESA in people who have ESA resistance (typically on haemodialysis and on high-dose ESA) and are having frequent transfusions when:

- All reversible causes of ESA resistance have been taken into account and excluded **and**
- The person's condition is otherwise 'stable' (without intercurrent illness such as infection) **and**
- The person is receiving adequate dialysis

Review the rate of red cell transfusion between 1 and 3 months after stopping ESA therapy. If the rate of transfusion has increased, consider restarting ESA therapy. **[new 2015]**

Footnotes

¹NICE is developing the guideline 'Blood transfusion' (publication expected November 2015).

²The [Medicines and Healthcare products Regulatory Agency \(MHRA\) guidance](#) (2007) 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. The MHRA advises that Hb levels greater than this should be avoided, and that patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia. Use of ESAs to achieve Hb levels greater than 120 g/litre is not consistent with UK marketing authorisations for ESAs. If such use is considered, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

³More than 175 international units per kg per week for haemodialysis population; more than 125 international units per kg per week for peritoneal dialysis population; more than 100 international units per kg per week for non-dialysis population. (Data provided by the UK Renal Registry and Guideline Development Group (GDG) expert opinion.)

⁴See recommendation *Diagnostic Tests to Determine Iron Status and Predict Response to Iron Therapy* for tests of choice to determine iron deficiency.

⁵Refer to the Summary of Product Characteristics for the prescription of individual iron preparations. At the time of publication (June 2015), intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information. Note that the marketing authorisation for ferumoxytol in the EU was withdrawn by the manufacturer in March 2015.

⁶There is no accepted definition of pre-dialysis. It is usually regarded to be CKD stages 4 and 5. Pre-dialysis includes people with a failing transplant and people having conservative management.

⁷The GDG considered this to be a maximum of 2 infusions. For adults, the GDG considered there would be a minimum of 500 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

⁸The GDG considered this to be more than 2 infusions. For adults, the GDG considered there would typically be 100 to 200 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

Definitions

Strength of Recommendations

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Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer...') are used when the GDG is confident that an intervention will not be of benefit for most patients.

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The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

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Clinical Algorithm(s)

An algorithm for diagnosis, correction, and maintenance of anaemia of chronic kidney disease (CKD) is provided in the full version of the guideline (see the "Availability of Companion Documents" field).

In addition, a National Institute for Health and Care Excellence (NICE) care pathway titled "Anaemia Management in People with Chronic Kidney Disease Overview" is available from the [NICE Web site](#).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Type of Studies

For most intervention reviews in this guideline, parallel randomised control trials (RCT) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the Guideline Development Group (GDG) believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C in the full guideline appendices (see the "Availability of Companion Documents" field) for full details on the study design of studies selected for each review question. Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted. For diagnostic reviews, RCTs and observational studies (case control studies

were excluded a priori) were included.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of anaemia in patients with chronic kidney disease (CKD), which may improve quality of life and prevent associated complications

Refer to the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for benefits of specific interventions.

Potential Harms

- The Guideline Development Group (GDG) discussed the implication of having false positives and false negatives in diagnostic tests. Poor sensitivity in a diagnostic test will result in more false negatives, which in turn will lead to people with iron-deficiency anaemia being undiagnosed and, therefore, untreated. In contrast, low specificity, leading to incorrect positive diagnoses (more false positives), will lead to unnecessary treatment, carrying a risk of unnecessary adverse events and higher costs.
- There are potential harms to transfusions in patients with anaemia of chronic kidney disease (CKD) (particularly fluid overload and sensitisation), although there are also benefits to treating anaemia during a period of concurrent illness when symptoms of anaemia may be impairing the recovery of the patient.
- For blood transfusions, the GDG considered the possibility of human leukocyte antigen (HLA) sensitisation, blood borne virus infection and transfusion reactions (for example, pyrexia or itch, or more severe allergic reactions which might require admission). High erythropoiesis-stimulating agent (ESA) dose, on the other hand, may be associated with higher overall mortality and cardiovascular complications. The majority of these adverse events would most likely have cost implications and may adversely affect quality of life.
- People with ESA hyporesponsiveness show evidence of increased morbidity and mortality compared with those who respond well to ESA therapy. Poor response to ESA therapy during the haemodialysis treatment period is thought to be associated with worse post-transplant long-term outcomes, including increased all-cause death and higher risk of graft failure. Little is known about the potential risks of maintaining people with CKD on high doses of ESA therapy while they are waiting for a kidney transplant. It is unclear whether high-dose ESA should be continued in people with ESA resistance in an attempt to limit the number of blood transfusions, or whether people should stop ESA treatment and be treated with transfusions alone. The adverse effects differ between the strategies and are likely to have implications for cost and quality of life.
- The administration of iron, whether oral or intravenous in preparation, carries risk and side effects to the patient, including gastrointestinal (GI) complications and sensitivity (including anaphylaxis). The benefits and harms are similar in both adult and paediatric populations. Oral iron often causes GI side effects, such as nausea, vomiting, constipation, diarrhoea and dark coloured stools. Sometimes the side effects are so unpleasant that the patient chooses to stop treatment. This is more likely in the paediatric population where compliance with oral iron therapy is more of a challenge. The side effects of intravenous iron are usually minimal, but may include the following: GI pains, including nausea and cramps; problems with breathing; skin problems, including rash; chest pain; low blood pressure; and anaphylaxis.
- The clinicians on the GDG also recognised that there is a greater risk of iron overload with intravenous therapy, making the monitoring of patients with serum ferritin important.

Refer to the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for harms of specific interventions.

Contraindications

Contraindications

- The Guideline Development Group (GDG) noted a more recent drug safety update from the Medicines and Healthcare Products Regulatory Agency (MHRA) issued in September 2014 regarding the contraindication of the use of ferumoxytol in patients with drug allergies and the requirement to administer it as an infusion and not by injection (<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452538>). In March 2015, due to this change in the mode of administration, the manufacturer of ferumoxytol (Rienso: Takeda UK Ltd) decided to withdraw the marketing authorisation for the product in the EU (<https://www.gov.uk/government/publications/medicines-company-led-recalls/rienso-30mgml-solution-for-infusion-takeda-uk-ltd-clda-15a02-16-march-2015>).
- Intravenous iron is contraindicated in people who have had a previous reaction to iron therapy.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- Remember that child maltreatment:
 - Is common
 - Can present anywhere
 - May co-exist with other health problems, including anaemia of chronic kidney disease (CKD)See the NICE guideline on [Child maltreatment](#) for clinical features that may be associated with maltreatment.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the [General Medical Council's Good practice in prescribing and managing medicines and devices](#) for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.
- Patients and healthcare professionals in England have rights and responsibilities as set out in the [National Health Service \(NHS\) Constitution for England](#) – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make in for med decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the [Department of Health's advice on consent](#), the [code of practice that accompanies the Mental Capacity Act](#) and the [supplementary code of practice on deprivation of liberty safeguards](#).
- NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in [Patient experience in adult NHS services](#).

- If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's [Transition: getting it right for young people](#) ².
- Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with anaemia of CKD. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.
- Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.
- The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

Implementation of the Guideline

Description of Implementation Strategy

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Diagnostic Evaluation and Assessment of Anaemia

Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months (every 1 to 3 months for people receiving haemodialysis).

- Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.
- If using % HRC is not possible, use reticulocyte haemoglobin (Hb) content (CHR; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.
- If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). **[new 2015]**

Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of chronic kidney disease (CKD). **[new 2015]**

Assessment and Optimisation of Erythropoiesis

Benefits of Treatment with Erythropoiesis-Stimulating Agents (ESAs)

Offer treatment with ESAs to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. **[2006]**

Optimal Hb Levels

The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.

- Typically¹ maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.
- To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range's limits). **[2011, amended 2015]**

ESAs: Monitoring Iron Status During Treatment

Offer iron therapy to people² receiving ESA maintenance therapy to keep their³:

- % HRC less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
- Reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
- Transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre)

The marker of iron status should be monitored every 1 to 3 months in people receiving haemodialysis.

In people who are pre-dialysis⁴ or receiving peritoneal dialysis, levels are typically monitored every 3 months. If these people have a normal full blood count there is little benefit in checking iron status. **[new 2015]**

Iron Therapy for People Who Are Iron Deficient and Not on ESA Therapy

Offer iron therapy to people² with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see "Optimal Hb Levels") offer intravenous iron therapy.
- For people who are receiving haemodialysis, offer intravenous iron therapy. Offer oral iron therapy to people who are receiving haemodialysis only if:
 - Intravenous iron therapy is contraindicated **or**
 - The person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy **[new 2015]**

Discuss the results of the iron therapy with the person or, where appropriate, with their family or carers and offer ESA therapy if needed (see "Benefits of Treatment with Erythropoietic Stimulating Agents [ESAs]"). **[new 2015]**

Iron Therapy for People Who Are Iron Deficient and Receiving ESA Therapy

Offer iron therapy to people² with anaemia of CKD who are iron deficient and who are receiving ESA therapy.

- Discuss the risks and benefits of treatment options. Take into account the person's choice.
- For adults and young people, offer intravenous iron therapy.
- For children who are receiving haemodialysis, offer intravenous iron therapy.
- For children who are not receiving haemodialysis, consider oral iron. If the child is intolerant of oral iron or target Hb levels are not reached within 3 months (see "Optimal Hb Levels"), offer intravenous iron therapy. **[new 2015]**

When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency⁵ intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:

- Preferences of the person with anaemia of CKD or, where appropriate, their family or carers

- Nursing and administration costs
- Cost of local drug supply
- Provision of resuscitation facilities

Intravenous iron administered at a low dose and high frequency⁶ may be more appropriate for all children² and for adults who are receiving in-centre haemodialysis. **[new 2015]**

Footnotes

¹The [Medicines and Healthcare products Regulatory Agency \(MHRA\)](#) [EPR](#) guidance (2007) 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. The MHRA advises that Hb levels greater than this should be avoided, and that patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia. Use of ESAs to achieve Hb levels greater than 120 g/litre is not consistent with UK marketing authorisations for ESAs. If such use is considered, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) [EPR](#) for further information.

²Refer to the Summary of Product Characteristics for the prescription of individual iron preparations. In particular, note that, at the time of publication (June 2015), intravenous iron products available in the UK did not have a UK marketing authorisation for all ages of children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) [EPR](#) for further information. Note that the marketing authorisation for ferumoxytol in the EU was withdrawn by the manufacturer in March 2015.

³See recommendation "Diagnostic Tests to Determine Iron Status and Predict Response to Iron Therapy" for tests of choice to determine iron deficiency.

⁴There is no accepted definition of pre-dialysis. It is usually regarded to be CKD stages 4 and 5. Pre-dialysis includes people with a failing transplant and people having conservative management.

⁵The Guideline Development Group (GDG) considered this to be a maximum of 2 infusions. For adults, the GDG considered there would be a minimum of 500 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

⁶The GDG considered this to be more than 2 infusions. For adults, the GDG considered there would typically be 100 to 200 mg of iron in each infusion. Refer to the Summary of Product Characteristics for the prescription of individual iron preparations.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Anaemia management in people with chronic kidney disease. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jun 3. 43 p. (NICE guideline; no. 8).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 (revised 2015 Jun 3)

Guideline Developer(s)

National Clinical Guideline Centre - National Government Agency [Non-U.S.]

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Guideline Committee

Guideline Development Group (GDG)

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*The GDG members listed are those for the 2015 update. For the composition of previous GDGs, see the full version of the guideline (see the "Availability of Companion Documents" field).

Financial Disclosures/Conflicts of Interest

See Section 4.4 in the original guideline document for declarations of interest made by members of the Guideline Development Group (GDG). All other members of the Group stated that they had no interests to declare. The conflicts of interest policy (2007) was followed until September 2014, when an updated policy was published.

See also Appendix B in the full guideline appendices (see the "Availability of Companion Documents" field) for interests declared by the 2015 GDG. See Appendix Z in the full guideline appendices for interests declared by the 2011 GDG.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Clinical Guideline Centre. Anaemia management in people with chronic kidney disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Feb. 38 p. (Clinical guideline; no. 114).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#). Also available for download in ePub and eBook formats from the [NICE Web site](#).

Availability of Companion Documents

The following are available:

- Anaemia management in people with chronic kidney disease. Full guideline. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 321 p. (NICE guideline; no. 8). Electronic copies: Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#).
- Anaemia management in people with chronic kidney disease. Appendices A-T from partial update 2015. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 250 p. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- Anaemia management in people with chronic kidney disease. Appendices U-Z and AA-HH from 2006 and 2011. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 355 p. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- Anaemia management in people with chronic kidney disease. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2015 Jun. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- Anaemia management in people with chronic kidney disease. Diagnostic tests to determine iron status table. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 1 p. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- Anaemia management in people with chronic kidney disease. Clinical audit tool. London (UK): National Institute for Health and Care Excellence; 2015 Jun. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- Anaemia management in people with chronic kidney disease. Costing statement. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 7 p. (NICE guideline; no. 8). Electronic copies: Available from the [NICE Web site](#).
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Electronic copies: Available from the [NICE Web site](#).

Patient Resources

The following is available:

- Anaemia management in people with chronic kidney disease. Information for the public. London (UK): National Institute for Health and Care Excellence; 2015 Jun. 12 p. (NICE guideline; no. 8). Electronic copies: Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#). Also available for download in eBook and ePub formats from the [NICE Web site](#).

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NGC Status

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