Anaemia Management in Chronic Kidney Disease

National clinical guideline for the management of anaemia in chronic kidney disease

Notes for consultation:
- Each paragraph is numbered to aid those wishing to comment on the draft, and will be simplified for publication. Recommendations will be numbered sequentially.
- The second consultation (18 April - 16 May 2006) will include audit criteria and the Information for the Public version of the guideline.
- “Reference ID” numbers are given in the reference list to aid the developers; these will be removed for publication.
- Some items in the document are highlighted in yellow to help editors update it prior to publication. The yellow highlighting will be removed for publication.
- This document is intended to emulate as far as possible the final published full guideline, but it will be professionally typeset and proofread at this final stage (September 2006).

Developed by

National Collaborating Centre for Chronic Conditions
at the Royal College of Physicians
1 Introduction

1.1 Definition of anaemia

1.2 Chronic Kidney Disease: Definition and prevalence

1.3 Prevalence of anaemia in patients with chronic kidney disease

1.4 Diabetes, CKD and anaemia

1.5 Causes of anaemia other than chronic kidney disease

1.6 Pathogenesis of anaemia associated with chronic kidney disease

1.7 How to use this guideline

1.8 Recommendations for children with anaemia of CKD

2 Methodology

2.1 About the guideline

2.2 Methodology

2.3 Disclaimer

2.4 Funding

3 Key Messages of the Guideline

3.1 Key Priorities for Implementation

3.2 Algorithms

3.3 Audit Criteria

4 Diagnostic evaluation & assessment of anaemia

4.1 Diagnostic Role of Hb Levels

4.2 Diagnostic Role of GFR

4.3 Diagnostic Tests to Determine Iron Status

4.4 Measurement of Erythropoietin

5 Management of Anaemia

5.1 Initiation of ESA Therapy in Iron-deficient Patients

5.2 Maximum Iron Levels in ACKD Patients

5.3 Initiation of ESA Therapy in Iron Replete Patients

5.4 Nutritional Supplements

5.5 Androgens

5.6 Hyperparathyroidism

5.7 Patient-Centred Care: ESAs

5.8 Patient Education Programmes

6 Assessment and Optimisation of Erythropoiesis

6.1 Benefits of Treatment with ESAs

6.2 Blood Transfusions

6.3 Comparison of ESAs

6.4 Early or Deferred ESA Treatment

6.5 Co-ordinating Care

6.6 Providing ESAs

6.7 ESAs: Optimal Route of Administration

6.8 ESAs: Dose and Frequency

6.9 Optimal Hb Levels

6.10 Optimum haemoglobin levels in children with anaemia of CKD

6.11 Adjusting ESA Treatment

6.12 Treating Functional Iron Deficiency: correction

6.13 Treating Functional Iron Deficiency: maintenance

6.14 ESAs: Monitoring Iron Status During Treatment

7 Monitoring of ACKD Treatment
7.1 Monitoring Iron Status ................................................................. 165
7.2 Monitoring Haemoglobin .............................................................. 167
7.3 Detecting ESA Resistance ............................................................ 168
7.4 Managing ESA Resistance ........................................................... 171
8 Research Recommendations .......................................................... 177
9 References .................................................................................. 205

Appendices:
Appendix A: Evidence-based clinical questions and literature searches
Appendix B: Scope
Appendix C: Health economic model: target haemoglobin in haemodialysis patients
Appendix D: Health economic calculation: route of administration
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Acknowledgements

The Guideline Development Group is grateful to the following people for their valuable contributions to the development of this guideline:

- Dr Bernard Higgins, Director, NCC-CC
- Ms Jane Ingham, Assistant Director, NCC-CC
- Ms Ester Klaeijsen, Administrator, NCC-CC
- Ms Jill Parnham, Manager, NCC-CC
- Colleagues working on the Health Technology Assessment of erythropoiesis-stimulating agents for cancer treatment-induced anaemia
**Preface**
To be completed for publication by the Director of the National Collaborating Centre.

**Glossary**

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKD</td>
<td>Anaemia of chronic kidney disease</td>
</tr>
<tr>
<td>bd</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CAPD</td>
<td>Continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CCr</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DS</td>
<td>Diagnostic study</td>
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<tr>
<td>EPO</td>
<td>Erythropoietin</td>
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<tr>
<td>Epoetin</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>ESA</td>
<td>Erythropoiesis stimulating agent</td>
</tr>
<tr>
<td>FID</td>
<td>Functional iron deficiency</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GPP</td>
<td>Good Practice Point</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<tr>
<td>Hct</td>
<td>Haematocrit</td>
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<tr>
<td>HD</td>
<td>Haemodialysis</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HRC</td>
<td>Hypochromic red cells</td>
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<tr>
<td>IP</td>
<td>Intraperitoneal</td>
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<tr>
<td>IV</td>
<td>Intravenously</td>
</tr>
<tr>
<td>LVH</td>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<tr>
<td>NSF</td>
<td>National Service Framework</td>
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<tr>
<td>PD</td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>PRCA</td>
<td>Pure red cell aplasia</td>
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<tr>
<td>PTX</td>
<td>Parathyroidectomy</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>RES</td>
<td>Reticuloendothelial system</td>
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<tr>
<td>ROC</td>
<td>Receiver operating characteristics</td>
</tr>
</tbody>
</table>
Guide to assessment scales

| Health related quality of life (HRQL) | A combination of a person’s physical, mental and social well-being; not merely the absence of disease. |
| Renal Quality of Life Profile | The SF-36 assesses functioning and well-being in any participant group with chronic disease. Thirty-six items in eight domains are included, which cover functional status, well-being, and overall evaluation of health. Scored range from 0 to 100, where a higher score indicates a better-perceived health status. |
| Stage 1 CKD | Creatinine clearance > 90 mL/min/1.73 m² |
| Stage 2 CKD | Creatinine clearance of 60–89 mL/min/1.73 m² |
| Stage 3 CKD | Creatinine clearance of 30–59 mL/min/1.73 m² |
| Stage 4 CKD | Creatinine clearance of 15–29 mL/min/1.73 m² |
| Stage 5 CKD | Creatinine clearance of <15 mL/min/1.73 m² or dialysis |
| Sickness Impact Profile (SIP) | SIP is a general quality of life scale. It consists of 136 items, which measure 12 distinct domains of quality of life. Participants identify those statements, which describe their experience. Higher scores represent greater dysfunction. |
| Visual Analogue Scale (VAS) | A non-graduated 100 mm vertical line ranging from “0=no pain” to “100=pain as bad as could be”. Patients indicate pain sensation by scoring on the vertical line with a horizontal dash |
| Verbal Descriptive Scale (VDS) | Divided into the following 6 categories: no pain, hardly any pain, mild pain, moderate pain, severe pain, unbearable pain. Patients tick the appropriate category on a questionnaire |

Definition of terms

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Absolute iron deficiency</td>
<td>Depletion in iron body stores</td>
</tr>
<tr>
<td>Adverse events</td>
<td>A harmful, and usually relatively rare, event arising from treatment.</td>
</tr>
<tr>
<td>Algorithm (in guidelines)</td>
<td>A flow chart of the clinical decision pathway described in the guideline.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>The process used to prevent advance</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
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<tr>
<td>Anaemia co-ordinator</td>
<td>A healthcare professional who follows a specialist-driven protocol of care for patients with ACKD</td>
</tr>
<tr>
<td>Audit</td>
<td>See “Clinical audit”</td>
</tr>
<tr>
<td>Before and after study</td>
<td>See “Observational study”</td>
</tr>
<tr>
<td>Bias</td>
<td>The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions which have been allocated.</td>
</tr>
<tr>
<td>Carer (caregiver)</td>
<td>Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.</td>
</tr>
<tr>
<td>Class of recommendation</td>
<td>See “Grade of recommendation”.</td>
</tr>
<tr>
<td>Clinical audit</td>
<td>A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.</td>
</tr>
<tr>
<td>Clinician</td>
<td>In this guideline, the term clinician means any health care professional.</td>
</tr>
<tr>
<td>Cochrane Review</td>
<td>A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.</td>
</tr>
<tr>
<td>Concordance</td>
<td>Concordance is a concept reflecting agreement between clinicians and patient on the best course of managing a disease, and adherence to that course until alternatives are agreed on and adopted.</td>
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<tr>
<td>Confidence interval (CI)</td>
<td>A range of values which contains the true value for the population with a stated “confidence” (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.</td>
</tr>
<tr>
<td>Cost-effectiveness analysis</td>
<td>An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.</td>
</tr>
<tr>
<td>Cost-effectiveness model</td>
<td>An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.</td>
</tr>
<tr>
<td>Cost-utility analysis</td>
<td>A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYS).</td>
</tr>
<tr>
<td>Cycling</td>
<td>See “Haemoglobin cycling”</td>
</tr>
<tr>
<td>Diagnostic study</td>
<td>Any research study aimed at evaluating the utility of a diagnostic procedure.</td>
</tr>
<tr>
<td>Erythropoiesis</td>
<td>Red blood cell production</td>
</tr>
<tr>
<td>Evidence-based health care</td>
<td>The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.</td>
</tr>
<tr>
<td>Follow up</td>
<td>An attempt to measure the outcomes of an intervention after the intervention has ended.</td>
</tr>
<tr>
<td>Functional iron deficiency</td>
<td>Inadequate iron mobilisation, which is incapable of meeting demands of erythropoiesis</td>
</tr>
<tr>
<td>Generalisability</td>
<td>The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine health care situations in the NHS in England and Wales.</td>
</tr>
<tr>
<td>Gold standard</td>
<td>See ‘Reference standard’</td>
</tr>
</tbody>
</table>
| Good Practice Point | Recommended good practice based on the
<p>| <strong>Grade (Class) of recommendation</strong> | All recommendations are assigned a grade (A,B,C,D or D(GPP)) according to the level of evidence the recommendation is based on (See “Level of evidence”). |
| <strong>Guideline development group (GDG)</strong> | An independent group set up by NICE to develop a guideline. They include healthcare professionals and person/carer representatives. |
| <strong>Haematocrit</strong> | Relative volume of blood occupied by red blood cells. |
| <strong>Haemoglobin cycling</strong> | Fluctuation of haemoglobin levels which may vary from patient to patient. |
| <strong>Hazard ratio (HR)</strong> | A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates. |
| <strong>Heterogeneity</strong> | In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect. |
| <strong>Homogeneity</strong> | In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review. |
| <strong>Inclusion criteria</strong> | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| <strong>Incremental cost</strong> | The cost of one alternative less the cost of another. |
| <strong>Incremental cost effectiveness ratio (ICER)</strong> | The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives. |
| <strong>Intention-to-treat analysis (ITT analysis)</strong> | An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention. |
| <strong>Level of evidence</strong> | A code (e.g. 1++, 1+,2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles. |
| <strong>Meta-analysis</strong> | A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Methodological limitations</td>
<td>Features of the design or reporting of a clinical study, which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>A statistical model for analysis of the relationship between two or more predictor (independent) and the outcome (dependent) variable.</td>
</tr>
<tr>
<td>National Collaborating Centre for Chronic Conditions (NCC-CC)</td>
<td>A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the Patient Involvement Unit at NICE, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians’ Patient and Carers Liaison Committee, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2000 to undertake commissions from NICE to develop clinical guidelines for the NHS.</td>
</tr>
<tr>
<td>National Health Service (NHS)</td>
<td>This guideline is written for the NHS in England and Wales.</td>
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<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>The proportion of people with a negative test result who do not have the disease.</td>
</tr>
<tr>
<td>Observational study</td>
<td>Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example cohort studies and case-control studies</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The “odds” is the ratio of non-events to events.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Measure of the possible results that may stem from exposure to prevention or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints.</td>
</tr>
<tr>
<td>P values</td>
<td>The probability that an observed difference could have occurred by chance. A P value of</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<td>-------------------------------------------</td>
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<tr>
<td>less than 0.05 is conventionally considered to be ‘statistically significant’.</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>The proportion of people with a positive test result who actually have the disease.</td>
</tr>
<tr>
<td>Pure red cell aplasia (PRCA)</td>
<td>Transitory arrest of erythropoiesis.</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Refers to the level of comfort, enjoyment, and ability to pursue daily activities.</td>
</tr>
<tr>
<td>Quality-of-life adjusted year (QALY)</td>
<td>A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.</td>
</tr>
<tr>
<td>Randomisation</td>
<td>Allocation of participants in a study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.</td>
</tr>
<tr>
<td>Randomised controlled Trial (RCT)</td>
<td>A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.</td>
</tr>
<tr>
<td>Reference standard (or gold standard)</td>
<td>An agreed desirable standard, for example a diagnostic test or treatment, against which other interventions can be compared.</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>The number of times more likely or less likely an event is to happen in one group compared with another.</td>
</tr>
<tr>
<td>Sample size</td>
<td>The number of participants included in a trial or intervention group.</td>
</tr>
<tr>
<td>Sensitivity (of a test)</td>
<td>The proportion of people classified as positive by the gold standard, who are correctly identified by the study test.</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.</td>
</tr>
<tr>
<td>Single blind study</td>
<td>A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.</td>
</tr>
</tbody>
</table>
| Specialist                                | A clinician whose practice is limited to a
<table>
<thead>
<tr>
<th>Definition</th>
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<tbody>
<tr>
<td>A particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.</td>
</tr>
<tr>
<td>Specificity (of a test)</td>
</tr>
<tr>
<td>The proportion of people classified as negative by the gold standard, who are correctly identified by the study test.</td>
</tr>
<tr>
<td>Stakeholder</td>
</tr>
<tr>
<td>Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.</td>
</tr>
<tr>
<td>Statistical power</td>
</tr>
<tr>
<td>In clinical trials, the probability of correctly detecting an effect due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being detected correctly.</td>
</tr>
<tr>
<td>Statistical significance</td>
</tr>
<tr>
<td>A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 (p&lt;0.05).</td>
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<tr>
<td>Systematic review</td>
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<tr>
<td>Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.</td>
</tr>
<tr>
<td>Washout period</td>
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<tr>
<td>The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.</td>
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<tr>
<td>Withdrawal</td>
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<tr>
<td>When a trial participant discontinues the assigned intervention before completion of the study.</td>
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</table>
THE DEVELOPMENT OF THE GUIDELINE
1 Introduction

1.1 Definition of anaemia

1.1.1.1 Internationally anaemia is defined as a state in which the quality and/or quantity of circulating red blood cells are below normal. Blood haemoglobin concentration serves as the key indicator for anaemia because it can be measured directly, has an international standard, and is not influenced by differences in technology. However, because haemoglobin values in healthy individuals within a population show a normal distribution a certain number of healthy individuals will fall below a given cut off point. Conventionally anaemia is defined as a haemoglobin concentration lower than the established cut off defined by the World Health Organization, and different biological groups have different cut off haemoglobin values below which anaemia is said to be present. This cut off figure ranges from 11g/dL for pregnant women and for children between 6 months and 5 years of age, to 12 g/dL for non-pregnan women, and to 13 g/dL for men (Table 1). No downward adjustment for the elderly is made for age. Although there is a theoretical basis for a fall in male haemoglobin levels with age, because of reduced testosterone production, this is clearly not the case for women. Furthermore there is accumulating evidence that anaemia reflects illness and is associated with adverse outcomes in the elderly. In the Cardiovascular Health Study 8.5 percent of participants were anaemic by WHO criteria. Those who were anaemic had a greater prevalence of associated comorbidity and significantly higher 11-year death rates than those without anaemia (57% and 39% respectively, p<0.001). The strongest correlates of anaemia were low body mass index, low activity level, fair or poor self-reported health, frailty, congestive heart failure, and stroke or transient ischemic attack. Anaemia was also associated with higher concentrations of creatinine, C-reactive protein, and fibrinogen, and lower levels of albumin and white blood cell count.

<table>
<thead>
<tr>
<th>Age or gender group</th>
<th>Haemoglobin below (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>6 months to 5 years</td>
<td>11.0</td>
</tr>
<tr>
<td>5 to 11 years</td>
<td>11.5</td>
</tr>
<tr>
<td>12 to 14 years</td>
<td>12.0</td>
</tr>
<tr>
<td>Non-pregnan females &gt;15 years</td>
<td>12.0</td>
</tr>
<tr>
<td>Men &gt;15 years</td>
<td>13.0</td>
</tr>
</tbody>
</table>
1.1.1.2 In addition to gender, age, and pregnancy status, other factors influence the cut off values for haemoglobin concentration. These include altitude, race, and whether the individual smokes. Although altitude is not a factor in patients in England ethnicity may be. Data from the United States show that healthy people of African extraction of all age groups at all times, except during the perinatal period, have haemoglobin concentrations 0.5-1.0 g/dL below those of whites, a difference independent of iron-deficiency and socio-economic factors.5-8

Haemoglobin concentration increases in smokers due to the formation of carboxyhaemoglobin, which has no oxygen transport capacity.10 The US Centers for Disease Control and Prevention have developed a smoking-specific haemoglobin adjustment to define anaemia in smokers (Table 2) and suggest that these values should be subtracted from observed haemoglobin values.11

<table>
<thead>
<tr>
<th>Amount smoked</th>
<th>Haemoglobin adjustment (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ - 1 pack/day</td>
<td>0.3</td>
</tr>
<tr>
<td>1 – 2 packs/day</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt; 2 packs/day</td>
<td>0.7</td>
</tr>
<tr>
<td>All smokers</td>
<td>0.3</td>
</tr>
</tbody>
</table>

1.2 Chronic Kidney Disease: Definition and prevalence

1.2.1.1 The Renal National Service Framework12,13 has adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of Chronic Kidney Disease (CKD). This classification divides CKD into 5 stages (Table 3) defined by evidence of kidney damage and level of renal function as measured by glomerular filtration rate (GFR).

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Normal or increased GFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Slight decrease in GFR, with other evidence of kidney damage</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderate decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe decrease in GFR, with or without other evidence of kidney damage</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Established renal failure</td>
</tr>
</tbody>
</table>
1.2.1.2 Stage 5 CKD may be described as established renal failure (also called end stage renal failure), and is CKD which has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) will be required to maintain life. Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only. Conventionally the total number of people receiving renal replacement therapy has been taken as a proxy measure for the prevalence of established renal failure. The NSF for Renal Services estimates that more than 27,000 people were receiving renal replacement therapy in England in 2001. Approximately one-half of these had a functioning transplant and the remainder were on dialysis. It is predicted that numbers will rise to around 45,000 over the next ten years. However, the most recently published Renal Registry Report (2004) highlights that in the UK there were over 37,000 patients receiving renal replacement therapy during 2003, a prevalence of 632 per million population. Of these 46% had a functioning transplant and the remainder were receiving dialysis treatment.

1.2.1.3 Data from the third US National Health and Nutrition Examination Survey (NHANES III) suggests that overall 11% of the population have some degree of kidney disease: 3.3% of the population are in stage 1 CKD, 3.0% in stage 2 CKD, 4.3% in stage 3 CKD, 0.2% in stage 4 CKD and 0.2% in stage 5 CKD. A similar population prevalence of stage 3-5 CKD has recently been described for England from data derived from primary care records. It is estimated that 4.9% of the population are in stage 3-5 CKD (estimated GFR less than 60 ml/min/1.73m²), although for methodological reasons this is probably an underestimate.

Is Chronic Kidney Disease a natural consequence of ageing?

1.2.1.4 Glomerular filtration rate has been shown to decline with age for many years. What is unclear however is to what extent these changes are a result of “normal ageing” or a result of disease processes? The cumulative exposure of the kidney to common causes of chronic kidney disease (atherosclerosis, hypertension, diabetes, heart failure, infection and nephrotoxins) increases with age and it is difficult to separate these from the ageing process.

1.2.1.5 Only one significant longitudinal study to date has addressed the issue of decreasing GFR with increasing age. In the Baltimore Longitudinal Study of Ageing, 446 community dwelling participants were followed over a period of up to 24 years. Their data suggests that the decline in GFR with increasing age is largely attributable to hypertension, possibly as a consequence of microvascular disease (Lindeman et al 1984). In the
absence of hypertension or other identifiable causes of renal disease, one third of older participants were noted to have stable GFR over a period of 20 years. In a small percentage of participants, GFR actually increased with ageing. Similarly, Fliser et al.\(^\text{17}\) in a cross-sectional study using insulin clearance have shown heart failure to be a significant factor in the decline of GFR with increasing age. Additionally, both heart failure and hypertension contributed to reductions in renal plasma flow and increases in the filtration fraction and renal vascular resistance. In a post-mortem study, Kasiske\(^\text{18}\) has demonstrated a relationship between the prevalence of sclerotic glomeruli and atherosclerotic vascular disease. Although twice as many patients with significant atherosclerosis had a history of hypertension as those with milder atherosclerosis, hypertension was not found to be independently predictive of glomerulosclerosis. Further evidence\(^\text{19}\) suggests that cumulative dietary protein intake is an important determinant of the fall in GFR. Studies such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have shown that the prevalence of reduced GFR is high in older hypertensive patients. Patients with moderate or severe reduction in GFR in the ALLHAT trial were more likely to have a history of cardiovascular disease and left ventricular hypertrophy compared to those with higher levels of GFR. Even modest reductions in GFR were independently associated with a higher prevalence of cardiovascular disease and left ventricular hypertrophy\(^\text{20}\).

1.2.1.6 The implications are that disease processes for renal disease in older people are similar to those of younger people and that a decline in renal function is not an inevitable consequence of ageing.

1.3 Prevalence of anaemia in patients with chronic kidney disease

1.3.1.1 The importance of anaemia in CKD has become increasingly apparent since the introduction of erythropoietin treatment into clinical practice in the late 1980s. However, until recently it has not been fully appreciated that anaemia begins to develop early in the course of CKD. NHANES III found lower levels of kidney function to be associated with lower haemoglobin levels and a higher prevalence and severity of anaemia [1803 /id].

Table 4: NHANES III data

<table>
<thead>
<tr>
<th>Stage of CKD</th>
<th>eGFR (mL/min/1.73m²)</th>
<th>Median Hb in men (g/dL)</th>
<th>Median Hb in women (g/dL)</th>
<th>Prevalence of anaemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60</td>
<td>14.9</td>
<td>13.5</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>13.8</td>
<td>12.2</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>12.0</td>
<td>10.3</td>
<td>33%</td>
</tr>
</tbody>
</table>

* - Hb<12.0 g/dL in men, Hb<11.0 g/dL in women.
1.3.1.2 In the UK information concerning the prevalence of anaemia in patients with CKD comes from 2 studies. The prevalence of diagnosed CKD, predicated by serum creatinine levels of $\geq 130 \text{ umol/L}$ in women and $\geq 180 \text{ µmol/L}$ in men, was 5,554 per million population (pmp), median age was 82 years (range, 18 to 103 years), and median calculated GFR was 28.0 mL/min/1.73m$^2$ (range, 3.6 to 42.8 mL/min/1.73 m$^2$) [1804 /id]. Data for haemoglobin levels were available for 85.6% of patients. Mean haemoglobin concentration was 12.1±1.9 g/dL, 49.6% of men had haemoglobin levels less than 12 g/dL and 51.2% of women had levels less than 11 g/dL. Furthermore, in 27.5% of patients identified, the haemoglobin level was less than 11 g/dL, equivalent to nearly 90,000 of the population based on 2001 population census figures. In a larger cross-sectional study abstracting data from 112,215 unselected patients with an age and sex profile representative of the general population haemoglobin level was weakly correlated with eGFR (Pearson correlation statistic 0.05727, p<0.001) 21. The population prevalence of stage 3-5 CKD in this study was estimated to be 4.9%. In those patients with stage 3-5 CKD the prevalence of anaemia, defined as a haemoglobin level less than 12 g/dL in men and post-menopausal women and less than 11 g/dL in pre-menopausal women, was 12.0%, haemoglobin level was less than 11 g/dL in 3.8%, equivalent to over 108,000 of the population based on 2001 population census figures.

1.4 Diabetes, CKD and anaemia

1.4.1.1 It has been known for some years that anaemia exists in patients with diabetes and CKD, and that this anaemia occurs early in the course of diabetic kidney disease and is associated with inappropriately low EPO concentrations 22,23. Ishimura et al 24 demonstrated that when those with type 2 diabetes (T2D) and CKD are compared to those with non-diabetic CKD, despite similarly advanced CKD and similar serum levels of EPO, those with DM (T2D) were significantly more anaemic.

1.4.1.2 Similar findings have also been demonstrated in people with Type 1 diabetes and CKD compared to those without diabetes 25. More recently, in a series of articles based on cross-sectional surveys of patients with diabetes, Thomas and colleagues demonstrated that at all levels of GFR anaemia was more prevalent in those with diabetes compared with the general population 26; that with increasing albuminuria the prevalence of anaemia was higher at each level of renal function 27, and that levels of EPO were inappropriately low in those with anaemia 28. Finally, in a report from the Kidney Early Evaluation Programme (KEEP) 29, the prevalence of anaemia in those with diabetes was significantly higher than in those without diabetes in stage 2 and 3 CKD (7.5% versus 5%,
p=0.015 and 22.2% versus 7.9%, p<0.001 respectively). Although the prevalence of anaemia was also higher in those with diabetes in stages 1 and 4 CKD the differences were not significant (8.7% versus 6.9% and 52.4% versus 50% respectively).

1.5 Causes of anaemia other than chronic kidney disease

1.5.1.1 Not all anaemia in patients with CKD will be 'renal anaemia' and causes of anaemia other than CKD should be actively looked for and excluded before a diagnosis of anaemia associated with CKD can be made (Table 5)

<table>
<thead>
<tr>
<th>Table 5. Other causes of anaemia in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic blood loss</td>
</tr>
<tr>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Vitamin B12 or Folate deficiency</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Chronic infection or inflammation</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Aluminium toxicity</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Haemolysis</td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
</tr>
</tbody>
</table>

1.5.1.2 Iron deficiency anaemia is the most common cause of anaemia worldwide, either due to negative iron balance through blood loss (commonly gastrointestinal or menstrual), or to inadequate intake which may be nutritional or related to poor gastrointestinal absorption. Studies in elderly patients (aged over 65 years) show that the 'anaemia of chronic disorders' predominates, accounting for 34% to 44% of causes. Iron-deficiency is the cause in 15% to 36% of cases and recent bleeding in 7.3%. Vitamin-B<sub>12</sub>/folate deficiency is the cause in 5.6% to 8.1%, myelodysplastic syndrome and acute leukaemia in 5.6% and chronic leukaemia and lymphoma-related disorders in 5.1%. Other haematological disorders (myelofibrosis, aplastic anaemia, haemolytic anaemia) are the cause in 2.8%, and multiple myeloma in 1.5%.
1.6 Pathogenesis of anaemia associated with chronic kidney disease

1.6.1 Although anaemia in patients with CKD may develop in response to a wide variety of causes erythropoietin deficiency is the primary cause of anaemia associated with CKD. Erythropoietin is predominantly produced by peritubular cells in the kidney and is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating erythropoietin in the face of anaemia (insert figure). Other factors in the genesis of renal anaemia include functional or absolute iron deficiency, blood loss (either occult or overt), the presence of uraemic inhibitors (e.g. parathyroid hormone, inflammatory cytokines), reduced half life of circulating blood cells, and deficiencies of folate or Vitamin B₁₂.

1.7 How to use this guideline

The purpose of this guideline is to support clinical judgement, not to replace it. This means the treating clinician should:

- take into consideration any contraindications in deciding whether or not to administer any treatment recommended by this guideline
- consider the appropriateness of any recommended treatment for a particular patient in terms of the patient’s relevant clinical and non-clinical characteristics.

Wherever possible, before administering any treatment the treating clinician should follow good practice in terms of

- discussing with the patient why the treatment is being offered and what health outcomes are anticipated
- highlighting any possible adverse events or side-effects that have been associated with the treatment
- obtaining explicit consent to administer the treatment.

For those recommendations involving pharmacological treatment, the most recent edition of the British National Formulary should be followed for the determination of:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics.

except in those cases where guidance is provided within the recommendation itself.
1.8 Recommendations for children with anaemia of CKD

This guideline gives recommendations for both adults and children. Where the recommendations are different for children, details are given separately:

- Section 6.9.7
- Section 6.12.6

2 Methodology

2.1 About the guideline

2.1.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for anaemia of chronic kidney disease (CKD)
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for anaemia of CKD
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.1.2 Scope

Purpose

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of anaemia in CKD to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE\textsuperscript{1,33}. The full scope is shown in Appendix B.
2.1.3 Audience
The guideline is intended for use with the following people or organisations:
- all healthcare professionals
- people with anaemia of CKD and their carers
- patient support groups
- commissioning organisations
- service providers.

2.1.4 Involvement of people with anaemia of CKD
The NCC-CC was keen to ensure the views and preferences of people with anaemia of CKD and their carers informed all stages of the guideline. This was achieved by:
- having a person with anaemia of CKD and a user organisation representative on the guideline development group
- consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.

2.1.5 Guideline limitations
These include:
- clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health)
- NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.

2.2 Methodology

2.2.1 Background
The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual and the methodology pack specifically developed by the NCC-CC for each chronic condition guideline (see http://www.rcplondon.ac.uk/college/ceeu/nccc_index.htm). The developers' role and remit is summarised in Figure 1.
Figure 1 – Role and remit of the developers

**National Collaborating Centre for Chronic Conditions (NCC-CC)**

The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Institute for Clinical Excellence (NICE).

A multiprofessional partners’ board inclusive of patient groups and NHS management governs the NCC-CC.

**NCC-CC Technical Team**

The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members:

- GDG group leader
- GDG clinical advisor
- Information scientist
- Research fellow
- Health economist
- Project manager
- Administrative personnel.

**Guideline Development Group**

The GDG met monthly for 12 months (January to December 2005) and comprised a multi-disciplinary team of professionals, service users (a person with anaemia of CKD), carers, and user organisation representatives who were supported by the technical team.

The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.

**Guideline Project Executive (PE)**

The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

The PE comprised of:

- NCC-CC Director
- NCC-CC Assistant Director
- NCC-CC Manager
- NICE Commissioning Manager
- Technical Team.

**Sign-off workshop**

At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE technical manual. A register is available from the NCC-CC for inspection upon request ncc-cc@rcplondon.ac.uk.
2.2.2 The process of guideline development

The basic steps in the process of producing a guideline are:

1. Developing clinical evidence based questions
2. Systematically searching for the evidence
3. Critically appraising the evidence
4. Incorporating health economic evidence
5. Distilling and synthesising the evidence and writing recommendations
6. Grading the evidence statements and recommendations
7. Agreeing the recommendations
8. Structuring and writing the guideline
9. Updating the guideline

1. Developing evidence based questions
   The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refine and approve these questions, which are shown in Appendix A.

2. Searching for the evidence
   The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers to inform detailed health economic work (e.g. modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

   Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

3. Appraising the evidence
   The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors however there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

   All procedures are fully compliant with the:

   - NICE methodology as detailed in the ‘Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers’ Manual ¹
4. Health economic evidence
Areas for health economic modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

5. Distilling and synthesising the evidence and developing recommendations
The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations\(^2\). The criteria for grading evidence and classifying recommendations are shown in Table 6.

Evidence tables are available on-line at (to be completed upon publication)
5. Grading the evidence statements and recommendations

Table 6:

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level</strong></td>
<td><strong>Type of evidence</strong></td>
</tr>
<tr>
<td>1++</td>
<td>High quality meta-analysis (MA), systematic reviews (SR) of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>MA, SR of RCTs, or RCTs with a high risk of bias*</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality SR of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies (for example case reports, case series)</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion, formal consensus</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
</tr>
</tbody>
</table>

Diagnostic study level of evidence and classification of recommendation was also included in the guideline.
7. Agreeing the recommendations

The sign-off workshop employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence-base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- five to ten key priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.

8. Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- Clinical introduction
  Sets a succinct background and describes the current clinical context
- Methodological introduction
  Describes any issues or limitations that were apparent when reading the evidence base
- Evidence statements
  Provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest
- Health economics
Presents, where appropriate, an overview of the cost effectiveness evidence-base

- From evidence to recommendation
  Highlights the debate of the guideline development group. This section sets out the Guideline Development Group (GDG) decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

- Recommendations
  Provides stand alone, action orientated recommendations.

- Evidence tables
  The evidence tables are not published as part of the full guideline but are available on-line at (to be completed upon publication - for consultation these are available at www.nice.org.uk). These describe comprehensive details of the primary evidence that was considered during the writing of each section.

9. Writing the guideline
The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed in Appendix X (to be completed prior to publication). Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

- Full version: Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at (to be completed upon publication)
- NICE version: Documents the recommendations without any supporting evidence. Available at (to be completed upon publication)
- Quick reference guide: An abridged version. Available online upon publication
- Information for the public: A lay version of the guideline recommendations. Available at www.nice.org.uk for 2nd consultation

NB: For consultation, drafts are online at www.nice.org.uk

10. Updating the guideline
Literature searches were repeated for all of the evidence based questions at the end of the GDG development process allowing any relevant papers published up until 28 September 2005 to be considered. Future guideline updates will consider evidence published after this cut-off date.
Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately four years after publication\(^1\).

### 2.3 Disclaimer

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 the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

### 2.4 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.
3 Key Messages of the Guideline

3.1 Key Priorities for Implementation

3.1.1 Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when the haemoglobin level is less than or equal to 11g/dL (or 10 g/dl if under 2 years of age) (C)

3.1.2 Patients with anaemia of CKD who are likely to benefit from ESAs in terms of quality of life and physical function should be offered treatment. (A)

3.1.3 In order that treatment is clinically effective, consistent, safe and patient centred, the prescriber should agree a plan with the patient, which is revised as the patient’s needs or circumstances change and which takes into account: (D (GPP))

- Providing a secure drug supply to the patient
- Flexibility of where the drug is delivered and administered
- The lifestyle and preferences of the patient
- Cost of drug supply
- A desire for self-care where appropriate

3.1.4 In adults with anaemia of chronic kidney disease, treatment should maintain stable haemoglobin (Hb) levels between 10.5 - 12.5 g/dL. Adjusting treatment should typically be considered when Hb rises above 12.0 or falls below 11.0 g/dL. C) Patient preferences, symptoms and comorbidity should be taken into account and the aspirational range and action thresholds revised accordingly. (C) For children aged 2 years and over, haemoglobin range should be maintained at the target range for adults. For children aged under 2 years, treatment should maintain stable haemoglobin levels between 10-11g/dl, reflecting the lower normal range in that age group. (D(GPP))

3.1.5 Age alone should not be a determinant for treatment of anaemia of CKD. (D(GPP))

3.1.6 In patients on maintenance therapy with ESAs, iron supplements should be given to keep:

- The serum ferritin between 200 and 500 µg/L in haemodialysis and between 100 and 500 µg/L in non-haemodialysis patients (D) and either
• The transferrin saturation level above 20% (unless ferritin >800 ug/L) (B)
  or
• percentage hypochromic red cells (%HRC) less than 6% (unless ferritin >800ug/L) (D(GPP))
3.2 Algorithms

3.2.1 Algorithm for diagnosis of renal anaemia

* - Test for FID with either:
  - ferritin and TSAT, or
  - ferritin and %HRC:

<table>
<thead>
<tr>
<th></th>
<th>Ferritin</th>
<th>TSAT %</th>
<th>MCV</th>
<th>HRC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional iron deficiency</td>
<td>Normal range, or raised</td>
<td>&lt; 20</td>
<td>Normal range</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Absolute iron deficiency</td>
<td>Low</td>
<td>&lt; 20</td>
<td>Low</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

see the iron management algorithm

see the ESA induction algorithm
### 3.2.2 Iron management algorithm

#### Iron Dosage Schedule

<table>
<thead>
<tr>
<th>Haemodialysis patients</th>
<th>Non-haemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction/Loading Dose</strong></td>
<td><strong>Maintenance Dose</strong></td>
</tr>
<tr>
<td>Either Iron sucrose 200 mg/week for 5 weeks or Iron Dextran 1g</td>
<td>Iron sucrose 50 mg/week or 100 mg/fortnight</td>
</tr>
</tbody>
</table>
Iron Management Algorithm – in an anaemic (Hb < 11g/dl) patient with CKD

Functional iron deficiency:
Ferritin ≥ 150-200 µg/L and either:
- TSAT < 20%
or
- %HRC > 6

If ferritin < 800 µg/L: **
- Administer IV iron *
  OR
  ESA + IV iron

Re-assess at 4 weeks

Hb < 11 g/dl
- Add ESA
- If on ESA, See Hb induction algorithm

Hb > 11 g/dl
- Reduce / stop IV iron
- If on ESA, See Hb maintenance algorithm
### 3.2.3 ESA Induction Algorithm – assumes Hb < 11g/dl

Throughout ESA induction:

In people with anaemia of chronic kidney disease, haemoglobin should be monitored:
- every 2-4 weeks in the induction phase of ESA treatment
- every 1-3 months in the maintenance phase of ESA treatment
- more actively after an ESA dose adjustment
- in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local health care systems

Be aware of side-effects and co-morbidities

---

**Flowchart Diagram:**

- **Ferritin ≤500 µg/L**
  - No, i.e. iron replete
- **Ferritin <200 µg/L**
  - Yes
    - TSAT < 20%
      - or %HRC > 6?
        - No: Hb >11 g/dL enter Hb maintenance algorithm and adjust ESA dose according to schedule
        - Yes: Hb rise < 1g after 4 weeks increase ESA dose according to schedule
  - No
    - ESA (s.c. or i.v.)
      - Hb >11 g/dL enter Hb maintenance algorithm and adjust ESA dose according to schedule

**Iron Dose Schedule:**

- IV iron
- ESA (s.c. or i.v.)
- ESA (s.c. or i.v.) + iron (i.v.) (See Sections 6.12 & 6.13)

**Hb Monitoring Schedule:**

- In people with anaemia of chronic kidney disease, haemoglobin should be monitored:
  - every 2-4 weeks in the induction phase of ESA treatment
  - every 1-3 months in the maintenance phase of ESA treatment
  - more actively after an ESA dose adjustment
  - in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local health care systems

- Be aware of side-effects and co-morbidities

---
3.2.4 Haemoglobin maintenance algorithm (assumes patient is receiving ESA and maintenance iv iron)
This is an example strategy. Treatment should be tailored to individual patients according to the guideline recommendations.
Consider also increasing ESA dosage frequency

Consider also reducing ESA dosage frequency

Ferritin <200 µg/L OR
Ferritin ≥200≤500µg/L and
TSAT < 20% (or %HRC > 6)

YES
Enter iron algorithm unless Hb > 12 g/dL
in which case follow instructions below

NO, i.e., iron replete

Hb < 11 g/dL
↑ESA dose according to
adjustment schedule
unless Hb increasing by
≥1g/dL/mth. If Hb
persistently low, see
**Poor responder
algorithm** Recheck Hb
g according to schedule.
Re-enter Hb
maintenance
algorithm

Hb 11 - 12 g/dL
If Hb rate of change
>1g/dL/mth consider
ESA dose
adjustment, otherwise no
change.
Re-enter Hb
maintenance
algorithm

Hb >12 - 15 g/dL
Consider stopping iv iron,
↓ESA dose according to
adjustment schedule unless
Hb falling by ≥ 1 g/dL.
Recheck Hb according to schedule
Re-enter Hb
maintenance
algorithm

Hb > 15 g/dL
Stop iv iron, halve
ESA dose**
Recheck Hb in 2
weeks
Re-enter Hb
maintenance
algorithm
ESA Adjustment Schedule – make adjustments based on absolute Hb level and/or rate of change of Hb >1g/dL/mth

1. Erythropoietins

<table>
<thead>
<tr>
<th>Current dose (units/week)</th>
<th>Increased dose (if single dose consider increasing dose frequency)</th>
<th>Decreased dose (consider reducing dose frequency, minimum weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>2000</td>
<td>Suspend</td>
</tr>
<tr>
<td>2000</td>
<td>3000</td>
<td>1000</td>
</tr>
<tr>
<td>3000</td>
<td>4000</td>
<td>2000</td>
</tr>
<tr>
<td>4000</td>
<td>6000</td>
<td>3000</td>
</tr>
<tr>
<td>6000</td>
<td>9000</td>
<td>4000</td>
</tr>
<tr>
<td>9000</td>
<td>12000</td>
<td>6000</td>
</tr>
<tr>
<td>12000</td>
<td>Seek advice</td>
<td>9000</td>
</tr>
<tr>
<td>&gt;12000</td>
<td>Seek advice</td>
<td>Seek advice</td>
</tr>
</tbody>
</table>

2. Darbepoietin

<table>
<thead>
<tr>
<th>Current dose (µg/week)</th>
<th>Increased dose (consider increasing dose frequency)</th>
<th>Decreased dose (consider reducing dose frequency, minimum monthly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>15</td>
<td>suspend</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>80</td>
<td>Seek advice</td>
<td>60</td>
</tr>
<tr>
<td>&gt;80</td>
<td>Seek advice</td>
<td>Seek advice</td>
</tr>
</tbody>
</table>

Frequency of Haemoglobin Monitoring

1. Haemodialysis patients
### Haemoglobin level and rate of change

<table>
<thead>
<tr>
<th>Haemoglobin level and rate of change</th>
<th>Monitoring frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 g/dL, rate of change ≤1 g/dL/month</td>
<td>4 weeks</td>
</tr>
<tr>
<td>&lt;11 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>11-12 g/dL, rate of change ≤1 g/dL/month</td>
<td>4 weeks</td>
</tr>
<tr>
<td>11-12 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>&gt;12-15 g/dL, rate of change ≤1 g/dL/month</td>
<td>4 weeks</td>
</tr>
<tr>
<td>&gt;12-15 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>&gt;15 g/dL</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

2. Peritoneal dialysis and pre-dialysis (including transplant) patients

<table>
<thead>
<tr>
<th>Haemoglobin level and rate of change</th>
<th>Monitoring frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 g/dL, rate of change ≤1 g/dL/month</td>
<td>4 weeks</td>
</tr>
<tr>
<td>&lt;11 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>11-12 g/dL, rate of change ≤1 g/dL/month</td>
<td>4-12 weeks</td>
</tr>
<tr>
<td>11-12 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>&gt;12-15 g/dL, rate of change ≤1 g/dL/month</td>
<td>4-12 weeks</td>
</tr>
<tr>
<td>&gt;12-15 g/dL, rate of change &gt;1 g/dL/month</td>
<td>2 weeks</td>
</tr>
<tr>
<td>&gt;15 g/dL</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>
3.2.5 Algorithm for patients with poor response to ESAs

ASSESS COMPLIANCE

Yes

Is there Reticulocytosis?

Investigate for blood loss/haemolysis

No

Is there Iron deficiency?
Fe < 150 mcg/l
Hypochromic red cells >2.5%

Yes

Start iv Iron*

No

Is dialysis adequate?
HD : Kt/v > 1.2 or URR > 65%
PD : Kt/v >1.7

Yes

Is there evidence of the following:
B12/ folate deficiency?
Myeloma?
Myelodysplastic?
Drug induced bone marrow suppression?
Haemoglobinopathies?
Infection/inflammation?
Hyperparathyroidism?
Aluminium or chloramine toxicity?

Yes

Investigate and treat appropriately
Consider referral to haematologist

No

Trial of high dose ESA

No

Optimise dialysis
3.3 Audit Criteria

To be included in the second consultation draft.
4 Diagnostic evaluation & assessment of anaemia

4.1 Diagnostic Role of Hb Levels

4.1.1 Clinical Introduction

4.1.1.1 Possible adverse effects of anaemia in patients with CKD include reduced oxygen utilisation, increased cardiac output and left ventricular hypertrophy (cardiac dilatation ± increased wall thickness) – Figure 2

4.1.1.2 It is also suggested that anaemia is associated with increased progression of CKD, reduced cognition and concentration, reduced libido and reduced immune responsiveness. How much these adverse effects translate into adverse outcomes such as impaired quality of life, increased hospitalisation, increased cardiovascular events and increased cardiovascular and all-cause mortality has been the subject of debate for several years. Large observational studies show an inverse association between haemoglobin levels and adverse outcomes but Level 1 evidence of an improvement in these outcomes with correction of anaemia is, to date, lacking. Part of the problem is that the available studies do not compare ‘no treatment of anaemia’ to treatment, but rather partial correction of anaemia to better correction.

Figure 2

4.1.1.3 Is it likely that adverse outcomes associated with anaemia are influenced by age, gender or ethnicity? The implications of this question are that we might adopt a differing strategy when correcting anaemia if there is evidence to dictate such an approach.

4.1.2 Methodological Introduction

4.1.2.1 A literature search identified longitudinal \textsuperscript{36,37,38,39}, before and after \textsuperscript{40,41,42,43} and cohort \textsuperscript{44,45,46,47} studies, conducted predominantly in haemodialysis patients.

4.1.2.2 Four studies \textsuperscript{48,49,50,51} did not meet quality criteria and were excluded from evidence statements.

Of note:
- No studies were found which specifically addressed the issues of gender and ethnicity and only one study was identified which stratified the study population according to age \textsuperscript{43}.
- Only two studies included populations over 80 years old \textsuperscript{37,46}.
- Not all studies reported gender and ethnicity of the participants. Some study participants were predominantly male \textsuperscript{41,42} or predominantly white \textsuperscript{45,46} or predominantly male and white \textsuperscript{49,52}. One study included a population that was 67% African American \textsuperscript{37}.
- The number of study participants varied greatly between 7 and over 60,000.

Health economics literature search

4.1.2.3 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects, therefore no health economic evidence statements are given.

4.1.3 Evidence Statements

Left ventricular hypertrophy

Predialysis patients

4.1.3.1 In a 1-year study (N=318) \textsuperscript{53}, a mean decrease in Hb of 0.5 g/dl from baseline of 12.8 ± 1.9 g/dl was found to be one of three factors (including systolic blood pressure and left ventricular (LV) mass index) that was associated with LV hypertrophy (odds ratio 1.32, 95% CI 1.1 to 1.59, P=0.004).

Level 2+
4.1.3.2 A decrease in LV mass index (P<0.01) was observed after raising Hct from 23.6 ± 0.5% (Hb ~ 7.8 g/dl) to 39.1 ± 0.8% (Hb ~ 13 g/dl) with epoetin over a time period of 12 months in a small sample (N=9) \(^{40}\).

Similarly, in another study (N=11) \(^{54}\), treatment with epoetin increased Hct levels from 26.3 ± 0.6% (Hb ~ 8.7 g/dl) to 34.4 ± 1.1% (Hb ~ 11.4 g/dl) at 3 months and 34.7 ± 1.3% (Hb ~11.5 g/dl) at 6 months. A reduction in LV mass index at month 6 (P<0.05), cardiac output (P<0.05), cardiac index (P<0.05), and an increase in total peripheral resistance (P<0.05) at months 3 and 6 of the study were observed.

**Level 3**

4.1.3.3 In two studies \(^{55,40}\), increased Hct levels with epoetin from 26.3 ± 0.6% (Hb ~ 8.7 g/dl) to 34.7 ± 1.3% (Hb ~11.5 g/dl) at 6 months \(^{56}\) and from 23.6 ± 0.5% (Hb ~ 7.8 g/dl) to 39.1 ± 0.8% (Hb ~ 13 g/dl) at 12 months \(^{40}\) found no changes in LV end-diastolic / systolic diameters, interventricular septum thickness, LV posterior wall thickness over 6 months \(^{57}\) or over 12-months \(^{40}\), or

**Level 3**

*Haemodialysis Patients*

4.1.3.4 In a 12-month study \(^{41}\) where Hb was increased from a baseline level of 6.3 ± 0.8 g/dl to 11.4 ± 1.5 g/dl by epoetin administration, a reduction in LV mass (P<0.001), LV end-diastolic volume (P=0.005) and LV end diastole (P=0.003) was found in patients with baseline LV mass above 210g...

**Level 3**

4.1.3.5 In the same study \(^{41}\), no significant changes were observed in echocardiography measurements of LV posterior wall, interventricular septum or mean wall thickness.

**Level 3**

4.1.3.6 In a small study (N=7) \(^{42}\) an increase in Hb from 9.8 ± 1.3 g/dl to 14.2 ± 0.6 g/dl using epoetin over a period of approximately 6 months found a significant reduction in cardiac output (P<0.01) and stroke volume (P<0.01), which was accompanied with a significant increase in total peripheral resistance (P<0.05). There was no change, however, in mean arterial pressure.

**Level 3**
Hospitalisation

Haemodialysis patients

4.1.3.7 Data from a cohort (N=66,761), stratified into increasing Hct levels and compared to an Hct level of 33 to 35% over a 1-year follow up period \(^{45}\) found the following:

Table 7

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>Hct &lt;30%</th>
<th>Hct 30 to 32%</th>
<th>Hct 33 to 35% (Ref)</th>
<th>Hct 36 to 38%</th>
<th>Hct ≥39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt;10 g/dl</td>
<td>1.42*</td>
<td>1.21*</td>
<td>1</td>
<td>0.78*</td>
<td>0.84*</td>
</tr>
<tr>
<td>Hb 10-10.7 g/dl</td>
<td>1.3*</td>
<td>1.17*</td>
<td>1</td>
<td>0.75*</td>
<td>0.88 (NS)</td>
</tr>
<tr>
<td>Hb 11 to 11.7 g/dl (Ref)</td>
<td>1.76*</td>
<td>1.3*</td>
<td>1</td>
<td>0.82*</td>
<td>0.62*</td>
</tr>
<tr>
<td>RR = relative risk</td>
<td>* significant</td>
<td>NS = not significant</td>
<td>Level 2+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1.3.8 In a two and a half-year follow-up study \(^{46}\), participants (N=50,579) were stratified into increasing Hct levels and compared to patients with the arbitrary reference of Hct 34 to 36% (N=22,192), see tables X:

Table 8: Adjusted relative risk of first hospitalisation due to any cardiac disease \(^{46}\)

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>≤30</th>
<th>31 to 33</th>
<th>34 to 36 (Ref)</th>
<th>37 to 39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>≤10</td>
<td>10.3 to 11</td>
<td>11.3 to 12 (Ref)</td>
<td>12.3 to 13</td>
<td>≥13.3</td>
</tr>
<tr>
<td>RR</td>
<td>1.18</td>
<td>1.07</td>
<td>1.00</td>
<td>0.92*</td>
<td>0.79*</td>
</tr>
<tr>
<td>95% CI</td>
<td>Not reported</td>
<td>Not reported</td>
<td>N/A</td>
<td>0.88 to 0.97</td>
<td>0.72 to 0.87</td>
</tr>
</tbody>
</table>

RR = relative risk
* significant
Level 2+
Table 9: Adjusted relative risk of first hospitalisation due to specific cardiac diseases  

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>34 to 36 (Ref)</th>
<th>37 to 39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>11.3 to 12 (Ref)</td>
<td>12.3 to 13</td>
<td>≥13.3</td>
</tr>
<tr>
<td>RR due to congestive heart failure, fluid overload or cardiomyopathy</td>
<td>1.00</td>
<td>0.85* (95% CI 0.77 to 0.95)</td>
<td>0.80* (95% CI 0.65 to 0.97)</td>
</tr>
<tr>
<td>RR due to ischemic heart disease, cerebrovascular disease or circulatory system disease</td>
<td>1.00</td>
<td>0.94 (NS) (95% CI 0.88 to 1.01)</td>
<td>0.81* (95% CI 0.70 to 0.93)</td>
</tr>
<tr>
<td>RR due to other cardiac diseases</td>
<td>1.00</td>
<td>0.95 (NS) (95% CI 0.87 to 1.05)</td>
<td>0.76* (95% CI 0.62 to 0.92)</td>
</tr>
</tbody>
</table>

RR = relative risk  
* significant  
NS = not significant  
Level 2+

Table 10: Adjusted relative risk of first hospitalisation for patients with cardiac comorbid conditions (N=45,166)  

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>34 to 36</th>
<th>37 to 39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>11.3 to 12</td>
<td>12.3 to 13</td>
<td>≥13.3</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>0.93*</td>
<td>0.79*</td>
</tr>
<tr>
<td>95% CI</td>
<td>N/A</td>
<td>0.89 to 0.98</td>
<td>0.71 to 0.87</td>
</tr>
</tbody>
</table>

* significant  
Level 2+

Table 11: Adjusted relative risk of hospitalisation for patients with Hct 37 to 39% without pre-existing cardiac disease (3 year follow up)  

| All-cause hospitalisation | 0.78 | <0.0001 |
| Any cardiac hospitalisation | 0.74 | 0.0005 |

Level 2+
**Mortality**

*Haemodialysis Patients*

4.1.3.9 Data from a cohort (N=66,761) were stratified into increasing Hct levels and compared to an arbitrary Hct level of 33 to 35% over a 1-year follow up period \(^{45}\):

Table 12

<table>
<thead>
<tr>
<th></th>
<th>Hct &lt;30%</th>
<th>Hct 30 to 32%</th>
<th>Hct 33 to 35% (Ref)</th>
<th>Hct 36 to 38%</th>
<th>Hct ≥39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR of all-cause mortality</td>
<td>1.74*</td>
<td>1.25*</td>
<td>1</td>
<td>0.99 (NS)</td>
<td>1.05 (NS)</td>
</tr>
<tr>
<td>RR of mortality from cardiac causes</td>
<td>1.57*</td>
<td>1.25*</td>
<td>1</td>
<td>0.96 (NS)</td>
<td>0.93 (NS)</td>
</tr>
<tr>
<td>RR of mortality from infections</td>
<td>1.92*</td>
<td>1.26*</td>
<td>1</td>
<td>1.08 (NS)</td>
<td>0.96 (NS)</td>
</tr>
</tbody>
</table>

* significant
NS=not significant

**Level 2+**

4.1.3.10 In a three year follow-up study \(^{46}\) participants (N=50,579) were stratified into Hct levels and compared to patients with the arbitrary reference of Hct 34 to 36% (N=22,192):

Table 13: Adjusted relative risk of mortality due to cardiac diseases \(^{46}\)

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>34 to 36 (Ref)</th>
<th>37 to 39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>11.3 to 12 (Ref)</td>
<td>12.3 to 13</td>
<td>≥13.3</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>0.92*</td>
<td>0.83*</td>
</tr>
<tr>
<td>95% CI</td>
<td>N/A</td>
<td>0.87 to 0.98</td>
<td>0.74 to 0.93</td>
</tr>
</tbody>
</table>

* significant

Table 14: Adjusted relative risk of all-cause mortality \(^{46}\)

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>34 to 36 (Ref)</th>
<th>37 to 39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>11.3 to 12 (Ref)</td>
<td>12.3 to 13</td>
<td>≥13.3</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>0.92*</td>
<td>0.86*</td>
</tr>
<tr>
<td>95% CI</td>
<td>N/A</td>
<td>0.88 to 0.96</td>
<td>0.80 to 0.93</td>
</tr>
</tbody>
</table>

* significant
Table 15: Adjusted relative risk of mortality for patients with Hct 37 to 39% without pre-existing cardiac disease

<table>
<thead>
<tr>
<th></th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.69</td>
<td>0.0002</td>
</tr>
<tr>
<td>Any cardiac death</td>
<td>0.69</td>
<td>0.0137</td>
</tr>
</tbody>
</table>

4.1.3.11 In one study (N=309)\textsuperscript{37}, no association was found between any Hct quartile (<33.4%; ≥ 33.4 to 35.73%; ≥ 35.74% to 38.55% and >38.55%) and survival over 18 months.

**Level 3**

4.1.3.12 In a 4-year study\textsuperscript{38}, renal units with >87% of patients achieving target Hct ≥33% (Hb ≥11 g/dl) had a lower mortality rate than those with <64% of patients achieving target Hct (P<0.0001). A 10% point increase in fraction of patients with Hct ≥33% (Hb ≥11 g/dl) was found to be associated with a 1.5% decrease in mortality (P=0.003).

**Level 3**
4.1.3.13 A retrospective cohort study with one year follow-up (N=75,283) found an increase in the age group to be associated with higher all-cause and cause-specific mortality. Female patients had better outcomes. When compared to white patients, black patients and other ethnic minorities had lower all-cause and cause-specific mortality.

In the same study, mortality data were compared to Hct 30 to <33% (Hb 10 to <11 g/dl):

<table>
<thead>
<tr>
<th>Hct</th>
<th>&lt;27% (N=9,130)</th>
<th>27 to &lt;30% (N=22,217)</th>
<th>30 to &lt;33% (REF) (N=33,122)</th>
<th>33 to &lt;36% (N=10,129)</th>
<th>1992 &amp; 1993 data 33 to &lt;36% (N=61,797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>&lt;9 g/dl (N=9,130)</td>
<td>9 to &lt;10 g/dl (N=22,217)</td>
<td>10 to &lt;11 g/dl (REF) (N=33,122)</td>
<td>11 to &lt;12 g/dl (N=10,129)</td>
<td>1992 &amp; 1993 data 11 to &lt;12 g/dl (N=61,797)</td>
</tr>
<tr>
<td>RR of all-cause death</td>
<td>1.33 95% CI 1.26-1.40</td>
<td>1.13 95% CI 1.08-1.17</td>
<td>1.00</td>
<td>0.96 95% CI 0.91-1.01 (P≤0.0956)</td>
<td>0.96 95% CI 0.92-0.99 (P=0.0385)</td>
</tr>
<tr>
<td>RR of cardiac death</td>
<td>1.25 95% CI 1.15-1.35</td>
<td>1.11 95% CI 1.05-1.17</td>
<td>1.00</td>
<td>0.97 95% CI 0.90-1.05</td>
<td>Not reported</td>
</tr>
<tr>
<td>RR of infectious death</td>
<td>1.53 95% CI 1.33-2.75</td>
<td>1.13 95% CI 1.02-1.26</td>
<td>1.00</td>
<td>1.02 95% CI 0.88-1.19</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Level 2+**
**MI, stroke and all-cause mortality**

**Pre-dialysis patients**

4.1.3.14 In one study (N=2,333)\textsuperscript{60}, hazard ratios for the composite outcome (MI, stroke and all-cause mortality) was significantly increased in individuals with anaemia (defined as Hb <12 g/dl or Hct <36% in women and Hb <13 g/dl in or Hct <39% in men) when compared to those without anaemia (hazard ratio 1.51; 95% CI 1.27 to 1.81).

**Quality of life**

**Haemodialysis Patients**

4.1.3.15 When evaluated in epoetin-treated patients (N=57)\textsuperscript{43} whose Hct increased from 21 ± 0.3% (Hb ~7 g/dl) at baseline to 28 ± 0.4% (Hb ~9.3 g/dl) at month 3 and 29 ± 0.4% (Hb ~9.7 g/dl) at month 6, quality of life was shown to improve by means of the Karnofsky scale (P=0.0001) and the global (P=0.0001), physical (P=0.0001) and psychosocial (P=0.0001) dimensions of the Sickness Impact Profile (SIP) questionnaire. This was further reinforced by linear regression between improvement of the SIP global score and final achieved Hct (29 ± 0.4%) (b coefficient 0.57, P<0.05, R\textsuperscript{2} 0.57).

**Effect of age on quality of life**

**Haemodialysis Patients**
4.1.3.16 In a sub-group analysis, of epoetin-treated patients divided into age ≥60 years (N=23) and <60 years (N=34), Hct levels were higher in the younger age group (P<0.05) 43. No differences were observed in improvements of quality of life scores using the Karnofsky scale or Sickness Impact Profile score when these age groups were compared 43. The same was true when patients were stratified into age <60 years (N=34) and ≥65 years (N=15) 43.

**Level 2+**

4.1.4 From Evidence to Recommendations

4.1.4.1 Data regarding the outcome of LVH was presented to the GDG. The longitudinal study by Levin et al (n= 466) illustrated that a mean Hb decrease of 0.5g/dl from 12.8 g/dl was associated with LVH suggesting that small changes in haemoglobin levels may make a difference to left ventricular growth 61. Two other studies demonstrated an association between decreasing left ventricular mass and increasing haematocrit levels 40,62 and one of these also found significant changes in other measures of cardiac function 63. Both of these studies 40,64 were based on small sample sizes (n= 9 and n= 11, respectively) and the GDG weighed these studies accordingly in their deliberations.

4.1.4.2 One small study (N=22) addressed patients receiving haemodialysis 41. The GDG noted that raising Hb levels from ~6 to ~11 g/dl improved cardiac function.

4.1.4.3 Two studies were appraised that examined the rate of progression of renal failure but these were excluded as underpowered by the GDG 40,65 and hence, no evidence statements were presented for this outcome.

4.1.4.4 A study analysing registry data found an increased risk of all-cause hospitalisation in haemodialysis patients treated with epoetin below the reference Hct level (< 30% and 30-<33%) 45. This study found a decrease in the risk of hospitalisation in patients treated above the reference level (36 - <39%) 45. The GDG noted that the greater hospitalisation rate could be a reflection of a sicker population and this may be other reason for the lower Hb level. It was also noted that the lowest haematocrit group required double the amount of EPO to reach this level, and as such, these participants may have a reduced health status.

4.1.4.5 The study by Moreno et al. 48 was excluded by the GDG due to a highly selective population (excluding both elderly and ill patients) and a lack of intention to treat analysis. Study 46 was also discussed and the group agreed to increase the grade to from 3 to 2+ as the study participants had been sub-divided according to Hct levels and the study had performed a multi-variate analysis of risk.

4.1.4.6 The GDG agreed that the evidence supported an association between decreased haematocrit and increased risk of hospitalisation.
4.1.4.7 The group felt that the evidence presented on mortality from one study suggested that there was an increase in mortality between Hct <30 to <33% (Hb levels ~10 –11g/dl) when compared to Hct 33 to 36% (Hb ~11-12g/dl). It was noted that this range spans the standard levels quoted in many guidelines. The data presented by two studies [52;1603] suggest that a Hb of < 11g/dl was the threshold below which there was an increased risk of mortality. However the GDG noted that these studies may not have accounted for confounding factors such as inter-current illness. The issue was also raised that there might be a reverse causality and that patients requiring high amounts of epoietin may be sicker and hence are more likely to require hospitalisation.

4.1.4.8 One study concluded that the haematocrit level was not a predictor of survival and that other markers of morbidity were more important. This data also suggested that confounding factors may be present that were not taken into account e.g. infection. This possibility was reflected in the study as the haematocrit levels were corrected for albumin. This study also suggested that males and females require different doses of EPO. Females appear to need more EPO than males.

4.1.4.9 Only one study was appraised that evaluated haemodynamic parameters but this was excluded for this outcome by the GDG as it was felt to be underpowered (N=7).

4.1.4.10 Regarding quality of life in haemodialysis patients (N= 57), a subgroup analysis of those over and under 60 years of age found a significant increase in quality of life scores associated with higher Hb levels in both age groups.

4.1.5 Recommendations

4.1.5.1 Management of anaemia should be considered in people with anaemia of chronic kidney disease (CKD) when the haemoglobin level is less than or equal 11g/dL (or 10 g/dl if under 2 years of age). (C)

See 3.2.1 for the associated algorithm.

4.2 Diagnostic Role of GFR

4.2.1 Clinical Introduction

4.2.1.1 Data from population studies such as NHANES III in the USA and the NEOERICA study in the UK suggest an increasing prevalence of anaemia with decreasing GFR level. A similar relationship between GFR and anaemia has also been demonstrated in population cohorts of people with diabetes. Although anaemia is common in people with diabetes it is also commonly unrecognised and undetected. The prevalence of anaemia in people with diabetes is increased at all levels of renal function in those with increased proteinuria/albuminuria, and it has been suggested that in people with diabetes, anaemia associated with CKD may occur earlier in the evolution of CKD when compared to people without diabetes. In investigating the evidence base, this section seeks to describe the
relationship between GFR and haemoglobin levels and provide guidance for clinicians with regard to the threshold level of GFR below which they should suspect that anaemia is associated with CKD.

4.2.2 Methodological Introduction

4.2.2.1 A literature search identified five studies investigating the association between GFR or creatinine clearance (CCr) with Hb/Hct levels in non-diabetic patients and four studies in diabetic patients.

4.2.2.2 Of note:
- Two studies were not limited to patients with CKD
- Two studies were conducted in selected patient populations and one study was conducted in children
- Patient populations in some studies were not stratified to diabetics and non-diabetics and where reported, the percentage of diabetics varied from 5% to 28% and to 64.4% All patients with CKD were in the untreated pre-dialysis stage, except for one study where some patients received oral iron (26%) and epoetin (12.8%) to treat their anaemia
- One study was conducted in people with type 2 diabetes, one in people with both type 1 and type 2 diabetes

Health economics literature search

4.2.3 Evidence Statements

Hb/Hct levels associated with different GFR or CCr levels in non-diabetic patients:

Table 17: GFR vs. Hb

<table>
<thead>
<tr>
<th>Median Hb level in women (g/dl)</th>
<th>Median Hb level in men (g/dl)</th>
<th>eGFR (ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5</td>
<td>14.9</td>
<td>60</td>
</tr>
<tr>
<td>12.2</td>
<td>13.8</td>
<td>30</td>
</tr>
<tr>
<td>10.3</td>
<td>12.0</td>
<td>15</td>
</tr>
</tbody>
</table>

Level 3

Table 18: GFR vs. Hb using >80 ml/min/1.73 m² as the reference value

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73 m²)</th>
<th>Women (N=8,495)</th>
<th>Men (N=3,560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80=ref</td>
<td>Difference in Hb (g/dl)</td>
<td>P value</td>
</tr>
</tbody>
</table>
Table 19: GFR vs. Hb

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73m²)</th>
<th>N</th>
<th>% of N with Hb ≤10 g/dl</th>
<th>% of N with Hb &gt;10 to ≤12 g/dl</th>
<th>% of N with Hb &gt;12 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>116</td>
<td>5.2%</td>
<td>21.6%</td>
<td>26.7%</td>
</tr>
<tr>
<td>≥30 to &lt;60</td>
<td>2,832</td>
<td>5.6%</td>
<td>35.9%</td>
<td>41.6%</td>
</tr>
<tr>
<td>≥15 to &lt;30</td>
<td>1,968</td>
<td>11%</td>
<td>42.6%</td>
<td>53.6%</td>
</tr>
<tr>
<td>&lt;15</td>
<td>298</td>
<td>27.2%</td>
<td>48.3%</td>
<td>75.5%</td>
</tr>
</tbody>
</table>

Level 3

Table 20: GFR vs. Hct

<table>
<thead>
<tr>
<th>Hct (%)</th>
<th>Estimated Hb (g/dl)</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>&lt;9</td>
<td>16.5 ± 6.8</td>
</tr>
<tr>
<td>28.0-29.9</td>
<td>9-&lt;10</td>
<td>17.9 ± 8.8</td>
</tr>
<tr>
<td>30.0-32.9</td>
<td>10-&lt;11</td>
<td>20.1 ± 7.6</td>
</tr>
<tr>
<td>33.0-35.9</td>
<td>11-&lt;12</td>
<td>22.0 ± 8.9</td>
</tr>
<tr>
<td>≥36</td>
<td>≥12</td>
<td>27.4 ± 7.9</td>
</tr>
</tbody>
</table>

Level 2+
Table 21: GFR vs. Hct in children (<21 years old)\textsuperscript{73}

<table>
<thead>
<tr>
<th>% of patients with Hct</th>
<th>≤30 %</th>
<th>31-32.9 %</th>
<th>&gt;33 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with estimated Hb (g/dl)</td>
<td>≤10</td>
<td>&gt;10-&lt;11</td>
<td>&gt;11</td>
</tr>
<tr>
<td>All patients</td>
<td>30.9 %</td>
<td>13.0 %</td>
<td>56.1 %</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m\textsuperscript{2})</td>
<td>&lt;10</td>
<td>62.9 %</td>
<td>11.3 %</td>
</tr>
<tr>
<td>10-25</td>
<td>48.1 %</td>
<td>16.8 %</td>
<td>35.1 %</td>
</tr>
<tr>
<td>25-50</td>
<td>25.7 %</td>
<td>13.3 %</td>
<td>61.0 %</td>
</tr>
<tr>
<td>50-75</td>
<td>13.1 %</td>
<td>8.1 %</td>
<td>78.7 %</td>
</tr>
</tbody>
</table>

2.4% of the study participants were treated with RBC transfusions after study entry. In addition, 26% of study participants received oral iron and 12.8% received epoetin during the course of the study.

**Level 2+**

*Hb/Hct levels associated with different GFR or CCr levels in diabetic patients*

**GFR vs. Hb**

4.2.2.4 In a retrospective cross-sectional study (N=28,862)\textsuperscript{80}, diabetes was recorded in 15.4% of patients with GFR <60 (stage 3-5 CKD). Of these, 15.3% were anaemic when defined as Hb <12 g/dl for females and <13 g/dl for males) and 3.8% were anaemic when defined as Hb <11 g/dl. **Level 3**

4.2.2.5 In a retrospective cross-sectional study in people with type 1 and 2 diabetes (N=820)\textsuperscript{81}, GFR was found to be an independent predictor of Hb (P<0.0001). Associations between Hb and GFR were continuously significant (P<0.05) at lower levels of GFR <70 vs. GFR 80-100. Hb was significantly lower in all patients with GFR <70 in both men and women (both P<0.0001). GFR >80 ml/min/1.73 m\textsuperscript{2} was not significantly associated with anaemia defined as Hb ≤11 g/dl (irrespective of sex) and Hb <13 g/dl in men and Hb <12 g/dl in women. **Level 3**
CCr vs. Hb

4.2.2.6 Type 2 diabetic patients with mild renal impairment (CCr 60-90 ml/min/1.73 m²)\(^{82}\), were approximately twice as likely to have anaemia as diabetic patients with normal renal function, defined as Hb <130 g/l in men and Hb <120 g/l in women (CCr >90 ml/min/1.73 m²) (P value not reported by the authors).

Level 3

GFR vs. Hb

4.2.2.7 Diabetes status and eGFR (ml/min/1.73m²) categories <30, 30-59, and 60-89 were significantly associated with an increased likelihood of anaemia, defined as Hb <12.0 g/dl for men & post-menopausal women (>50 years old) and Hb <11.0 for pre-menopausal women (≤50 years old) using eGFR ≥90 as the reference\(^{83}\).

Level 3

4.2.2.8 In the same study\(^ {84}\), when eGFR was divided into 10 ml/min/1.73m² strata, the prevalence of anaemia by diabetes status was statistically significant at each of the categories between 31-60 ml/min/1.73m², but did not differ for any other categories.

4.2.2.9 In addition, in men with diabetes, significantly lower Hb levels were observed at all eGFR categories <60 ml/min/1.73m², whereas among women with diabetes and all study participants without diabetes (both men & women), significantly lower Hb levels were not apparent until more advanced levels of kidney impairment (eGFR <31 ml/min/1.73m²).

Level 3

4.2.4 From Evidence to Recommendations

4.2.2.10 The comparison of diabetic and non-diabetic populations was based on a clinical perception that the diabetic population was at risk of developing anaemia of CKD at an earlier stage. The GDG felt that this perception had arisen partly due to the selected patient populations in many of the studies, the cross-sectional nature of the studies, and the lack of standardisation of estimates of renal function used in the various studies.

4.2.2.11 The current clinical perception of the GDG is that although there was a correlation between diabetes and the anaemia of CKD, the prevalence of anaemia in those with diabetes appeared greater than those without at higher levels of GFR. Within whole population studies there were similar mean haemoglobin levels between those with diabetes and those without across a range of GFRs.

4.2.2.12 It was agreed that setting a threshold value of eGFR of 60 ml/min/1.73m² (the boundary between Stage 2 and Stage 3 CKD) would be of use in helping clinicians decide whether to consider anaemia of CKD as a cause of the anaemia, although
there were some concerns about whether the error around a single measurement would make this a suitable recommendation.

4.2.2.13 It was felt there was some merit in an empirical statement that supported setting an eGFR of $< 60 \text{ ml/min/1.73m}^2$ which should alert a clinician to consider anaemia of CKD as the cause, and that other causes were likely in patients with a eGFR $> 60$.

### 4.2.5 Recommendations

4.2.5.1 An estimated glomerular filtration rate (eGFR) of $< 60 \text{ ml/min/1.73m}^2$ should trigger investigation into whether anaemia is due to CKD. When eGFR is $\geq 60 \text{ ml/min/1.73m}^2$ the anaemia is more likely to be related to other causes. (D)

See 3.2.1 for the associated algorithm.
4.3 Diagnostic Tests to Determine Iron Status

4.3.1 Clinical Introduction

4.3.1.1 The purpose of the evidence review in this section was to attempt to identify the best combination of tests to determine iron status in patients with CKD.

4.3.1.2 The aim of determining iron status is to be able to identify which patients need iron supplementation, as well as those who do not. Although absolute iron deficiency may occur in patients with chronic kidney disease we more frequently identify what is termed ‘functional iron deficiency’. Although iron stores may seem adequate when measured by conventional indices of iron status, there may be a lack of ‘freely available iron’ for effective erythropoiesis in the bone marrow.

4.3.1.3 There is a lack of well-accepted ‘gold standard’ tests for determining iron deficiency in the setting of CKD. While bone marrow iron stores are often regarded as the best indicator of iron status, this is not universally accepted and taking a bone marrow sample is invasive, relatively time consuming and expensive. The frequent co-existing inflammatory or infective problems in patients with CKD can complicate the interpretation of iron status parameters. For example, serum ferritin is a good marker of storage iron and decreases in iron deficiency states. However, it is also an acute phase reactant, which means it is frequently raised in inflammatory conditions, such as CKD, regardless of the iron status. All the available tests of iron status are subject to similar limitations and detailed discussion is beyond the scope of this guideline. The British Committee for Standards in Haematology is producing a document ‘Evaluation of Iron Status’, which will deal comprehensively with these issues (although not specifically in the setting of CKD). It is accepted that no single parameter can determine iron status. Serum ferritin shows the best correlation with bone marrow iron scores and iron deficiency should be ascertained by a combination of serum ferritin (storage iron) and tests of iron utilisation (reticulocyte haemoglobin content, % hypochromic red cells, transferrin saturation, ZPP).

4.3.1.4 In patients without CKD normal serum ferritin levels are over 20 µg/L, but in those with CKD a value of 100 µg/L is considered to be the lower limit of normal to allow for the associated mild inflammatory state. The percentage of hypochromic red cells (HRC) directly reflects the number of red blood cells with suboptimal levels of haemoglobin content (<28 g/dL) and may be determined using certain analysers. HRC <2.5% is normal and HRC >10% indicates definite functional iron deficiency. Measurement must be on a fresh sample (<4 hours after the blood is withdrawn) because of storage artefact. Reticulocyte haemoglobin content (CHr) may also be measured by certain analysers and is derived from the simultaneous measurement of volume and haemoglobin concentration in reticulocytes. Levels indicating functional iron deficiency depend on the analyser used. Transferrin saturation
(TSAT) is a derived value and may be calculated from serum iron $\times 100$/Total iron binding capacity; or serum iron ($\mu g$/dL) $\times 70.9$ divided by serum transferrin (mg/dL). Transferrin levels are also influenced by inflammation and nutrition (correlating with serum albumin levels). A TSAT of $<20\%$ suggests functional iron deficiency.

### 4.3.2 Methodological Introduction

#### 4.3.2.1
A literature search identified studies which addressed (i) the ability of tests to detect iron deficiency\textsuperscript{85,86,87} and (ii) the ability of tests to predict the response to intravenous iron supplementation in patients with predefined iron parameters receiving epoetin\textsuperscript{88,89,90,91,92,93}.

#### 4.3.2.2
Of the six studies looking at the response to intravenous iron, five studies predefined the patient population to whom iron was given as being iron deficient (see table X below). In one study\textsuperscript{91} the response to intravenous iron was used to define the prior iron status. No study addressed the issue of loading with iron prior to epoetin administration.

**Table 22: Definition of detection of iron deficiency**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Iron dosing regimen</th>
<th>Definition of positive response to iron administration, i.e. iron-deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>1g infusion (over 2 hours)</td>
<td>Erythropoietic response to the iron treatment; a sustained increase in corrected reticulocyte index of 1 base point (i.e. from 1.7% to 2.7%) within 2 weeks</td>
</tr>
<tr>
<td>90</td>
<td>500mg to 1g infusion (over 1 hour)</td>
<td>$&gt;5%$ increase in Hct, 4 weeks after administration</td>
</tr>
<tr>
<td>91</td>
<td>$\sim$1g over 8 weeks</td>
<td>Hb response $\geq 15%$ of baseline value</td>
</tr>
<tr>
<td>94</td>
<td>240mg iron colloid over 2 weeks</td>
<td>Not reported</td>
</tr>
<tr>
<td>93</td>
<td>1.5g over 41.7 weeks</td>
<td>\begin{itemize} \item Reduction in weekly epoetin dose of at least 30 units/kg/week in the subsequent 12 weeks whilst maintaining a target Hct of 30 to 33% \item Reduction in weekly epoetin dose of at least 60 units/kg/week in the subsequent 12 weeks whilst maintaining a target Hct of 30 to 33% \end{itemize}</td>
</tr>
<tr>
<td>88</td>
<td>1g over 10 HD</td>
<td>\begin{itemize} \item $\geq 5%$ increase in Hct or a decrease in \end{itemize}</td>
</tr>
<tr>
<td>treatments</td>
<td>epoetin dose if the Hct increased to more than 38%</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

HD = Haemodialysis
4.3.3 Evidence Statements

Studies where iron was administered

A variety of studies looked at the utility of a number of markers of iron status as indicators of iron deficiency following iron administration. Response to iron administration variably defined by increase in haemoglobin level and/or reduction in erythropoietin dose.

Table 23:

<table>
<thead>
<tr>
<th>Reference</th>
<th>N (range)</th>
<th>Iron test (cut-off range in studies)</th>
<th>Test cut-off value</th>
<th>Sensitivity</th>
<th>Test cut-off value</th>
<th>Specificity</th>
<th>Evidence hierarchy</th>
</tr>
</thead>
<tbody>
<tr>
<td>[174;130;148;1617]</td>
<td>32-136</td>
<td>Serum ferritin (50 to 400 µg/L)</td>
<td>&lt;50 µg/L</td>
<td>19.6%</td>
<td>&lt;100 µg/L</td>
<td>30-78.4%</td>
<td>DSII [174;130;148]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;100 µg/L</td>
<td>35.3-71.4%</td>
<td>&lt;50 µg/L</td>
<td>94.6%</td>
<td>DSIII 95</td>
</tr>
<tr>
<td>[130;174]</td>
<td>32 and 51</td>
<td>%HRC (&gt;4% to &gt;10%)</td>
<td>&gt;4%</td>
<td>86.3%</td>
<td>&gt;4%</td>
<td>78.4%</td>
<td>DSII [174;130]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;10%</td>
<td>42.8 and</td>
<td>&gt;10%</td>
<td>80 and 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45.1%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[130;148;174;1610;1617]</td>
<td>32-136</td>
<td>TSAT (&lt;12% to &lt;28%)</td>
<td>&lt;20%</td>
<td>57.1-74%</td>
<td>&lt;20%</td>
<td>36-80%</td>
<td>DSII [130;148;174;1610]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DSIII 93</td>
</tr>
<tr>
<td>[148;174]</td>
<td>17 and 51</td>
<td>Serum ferritin</td>
<td>Serum</td>
<td>33% and</td>
<td>Serum ferritin</td>
<td>67% and</td>
<td>DSII [148;174]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100µg/L and TSAT (&lt;20%)</td>
<td>ferritin &lt;100µg/L and TSAT &lt;20%</td>
<td>68.6%</td>
<td>&lt;100µg/L and %TSAT (&lt;20%)</td>
<td>60.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>-------</td>
<td>----------------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32-94 Ret Hb (&lt;26 pg to &lt;32.5 pg)</td>
<td>&lt;26 pg</td>
<td>100%</td>
<td>&lt;26 pg</td>
<td>80%</td>
<td>DSII [130;174;1610]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZPP (&gt;52 and &gt;90 µmol/mol haem)</td>
<td>&gt;52 µmol/mol haem</td>
<td>80.6%</td>
<td>&gt;52 µmol/mol haem</td>
<td>68.7%</td>
<td>DSII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 %HRC (&gt;6%) and other tests</td>
<td>%HRC &gt;6% and Ret Hb ≤29 pg</td>
<td>86.3%</td>
<td>%HRC &gt;6% and Ret Hb ≤29 pg</td>
<td>93.2%</td>
<td>DSII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%HRC &gt;6% and serum ferritin &lt;50 ng/ml</td>
<td>82.4%</td>
<td>%HRC &gt;6% and serum ferritin &lt;50 ng/ml</td>
<td>89.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%HRC &gt;6% and TSAT &lt;19%</td>
<td>96.1%</td>
<td>%HRC &gt;6% and TSAT &lt;19%</td>
<td>74.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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<td>------------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%HRC &gt;6% and ZPP &gt;52 μmol/mol haem</td>
<td>94.9%</td>
<td>%HRC &gt;6% and ZPP &gt;52 μmol/mol haem</td>
<td>71.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%HRC &gt;6% and STR &gt;1.5 mg/dL</td>
<td>85.7%</td>
<td>%HRC &gt;6% and STR &gt;1.5 mg/dL</td>
<td>73.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRC = hypochromic red cells
TSAT = transferrin saturation
Ret Hb = reticulocyte haemoglobin content
ZPP = erythrocyte zinc protoporphyrin
STR = serum transferrin receptor
PPV = positive predictive value
NPV = negative predictive value
### No Iron Administration

**Table 24:**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N (range)</th>
<th>Iron test (cut-off range in studies)</th>
<th>Test cut-off value</th>
<th>Sensitivity</th>
<th>Test cut-off value</th>
<th>Specificity</th>
<th>Evidence hierarchy</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>63</td>
<td>STR (1.39 µg/ml to 3.5 µg/ml)</td>
<td>STR 1.39 µg/ml</td>
<td>84%</td>
<td>STR 1.39 µg/ml</td>
<td>30%</td>
<td>DSlb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STR 3.5 µg/ml</td>
<td>38%</td>
<td>STR 3.5 µg/ml</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[140 /id]</td>
<td>25</td>
<td>Bone marrow examination (BME) vs. other tests</td>
<td>BME vs. Serum ferritin &lt;200 µg/L</td>
<td>41%</td>
<td>BME vs. Serum ferritin &lt;200 µg/L</td>
<td>100%</td>
<td>DSlb</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BME vs. TSAT &lt;20%</td>
<td>88%</td>
<td>BME vs. TSAT &lt;20%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>[1615 /id]</td>
<td>36</td>
<td>TSAT vs. other tests</td>
<td>TSAT &lt;15% vs. Ret Hb &lt;26 pg</td>
<td>73</td>
<td>TSAT &lt;15% vs. Ret Hb &lt;26 pg</td>
<td>100</td>
<td>DSII</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TSAT &lt;15% vs. %HRC &gt;2.5%</td>
<td>91</td>
<td>TSAT &lt;15% vs. %HRC &gt;2.5%</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSAT &lt;15% vs. %HRC &gt;5%</td>
<td>91</td>
<td>TSAT &lt;15% vs. %HRC &gt;5%</td>
<td>62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.3.4 From Evidence to Recommendations

4.3.4.1 The group compared the tests based on the sensitivity, specificity and receiver operator characteristics. The group did not use the negative- or positive- predictive values as it was considered that these values were only truly representative of the study population included in each trial.

4.3.4.2 These iron supplementation studies have dealt with iron deficiency or ‘functional iron deficiency’ (where storage iron may be adequate, but iron utilisation in red cell production is defective). The studies have not addressed the issues of: whether iron supplementation could be beneficial in patients having epoetin even with apparently normal iron status; or when should iron supplementation should be stopped because of a possible risk of iron overload.

4.3.4.3 Reticulocyte Hb content and the percentage of hypochromic red cells were also discussed. Neither of these tests is widely available and both are currently under a commercial patent. With respect to reticulocyte Hb content, the GDG felt that although this looked like a sensitive test, the cut-off for this test was a Hb content of <26pg, this was considered very low as the normal range is reported to be 31 – 33pg. The GDG noted that the percentage of hypochromic red cells provided the best sensitivity and specificity from a single test.

4.3.4.4 In general, the GDG noted that tests for serum ferritin and transferrin saturation were the most widely used but that they had poor sensitivity and specificity. The GDG noted however that these tests were both cheap and widely available. It was noted that serum ferritin was the only test addressing iron storage while the other tests reviewed in the evidence assessed iron utilisation. The GDG agreed that no single test was adequate to determine iron status. Serum ferritin showed the best correlation with bone marrow iron scores. Iron deficiency should be ascertained by a combination of serum ferritin (storage iron) and tests of iron utilisation (reticulocyte haemoglobin content, % hypochromic red cells, transferrin saturation, ZPP).
4.3.5 Recommendations

4.3.5.1 In patients with CKD, serum ferritin should be used to assess absolute iron deficiency. (A(DS))

4.3.5.2 If serum ferritin is below the normal range, patients with stage 5 CKD should be considered iron deficient, and patients with stage 3-4 CKD may also be iron deficient. (D(GPP))

4.3.5.3 In patients with CKD and serum ferritin levels greater than 100, functional iron deficiency (i.e. those patients who will benefit from intravenous iron therapy) should be defined by:

- percentage of hypochromic red cells > 6%, where the test is available. (B (DS))
- transferrin saturation < 20%, when the measurement of the percentage of hypochromic red cells is not available (B (DS))

See 3.2.1 for the associated algorithm.

4.4 Measurement of Erythropoietin

4.4.1 Clinical Introduction

4.4.1.1 Although anaemia in CKD may develop in response to a wide variety of causes, erythropoietin (EPO) deficiency is the primary cause of renal anaemia. Predominantly produced by peritubular cells in the kidney, EPO is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating EPO in the face of anaemia (Figure 3).
4.4.1.2 We know that anaemia develops early in the course of chronic kidney disease. NHANES III found lower levels of kidney function to be associated with lower haemoglobin levels and a higher prevalence and severity of anaemia [1803 /id]. The prevalence of anaemia, defined as haemoglobin levels of less than 12 g/dL in men and less than 11 g/dL in women, increased from 1 percent at an estimated GFR of 60 mL/min per 1.73 m², to 9 and 33 percent at estimated GFRs of 30 and 15 mL/min per 1.73 m² respectively. Using the same definition of anaemia it is suggested that in people with diabetes and CKD the prevalence of anaemia in stage 2 and 3 CKD is greater than in those without diabetes 96. In this study of 5380 participants from the Kidney Early Evaluation Program 22% of those with CKD stage 3 and diabetes had anaemia compared with 7.9% of those with stage 3 CKD alone (p<0.001). In stage 2 CKD 7.5% of those with diabetes were anaemic compared with 5.0% of those without diabetes (p=0.015). In people with diabetes the prevalence of anaemia at all levels of GFR is greater with increasing levels of albuminuria 97.
4.4.1.3 When patients with diabetes and CKD are stratified into those more likely to be iron-replete (TSAT>16%) and those less likely to be iron-replete (TSAT<16%) anaemia is associated with a relative lack of EPO response in those with TSAT>16% 28.

4.4.1.4 In patients with less advanced CKD there may be some uncertainty with respect to whether or not the anaemia is associated with lack of EPO, and this may be particularly so in transplanted patients in whom immunosuppression may also play a role in suppressing the bone marrow response. In these patients knowledge of serum erythropoietin levels may be beneficial and the evidence review in this section seeks to address this.

4.4.2 Methodological Introduction

4.4.2.1 One cohort study 98, six cross-sectional studies 99,25,100, 101,102,28 and two longitudinal studies, prospective 103 and retrospective 104, which examined the association between serum erythropoietin with Hb levels or renal function were identified in a literature search.

4.4.2.2 Of note:
- The studies comprised selected and unselected participants
- Of the three studies conducted in people with diabetes, the study populations consisted of people with type 2 diabetes without nephropathy 104, selected people with type 1 diabetes with diabetic nephropathy in the absence of advanced renal failure 25; people with Type 1 and 2 diabetes 28
- Other causes of anaemia were explicitly ruled out in some studies 104, 25, 103, 100, 98
Where reported, anaemia was defined as <13 g/l for males and <11.5 g/l for females \(^{104}\); Hb \(\leq 11.5\) g/dl for women and 12.0 g/dl for men \(^{25}\); Hb <11 g/dl \(^{100}\), Hb < 12 g/dl for women and Hb <13 g/dl for men \(^{28}\)

**Health economics literature search**

4.4.2.3 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects, therefore no health economic evidence statements are given.

### 4.4.3 Evidence Statements

**Adults with diabetes**

4.4.3.1 In people with type 2 diabetes *without nephropathy* (N=62) a significant negative correlation between serum EPO and Hb levels was found \((r^2=0.612, P=0.01)\) \(^{104}\).

**Level 3**

4.4.3.2 In contrast to the above finding, a study in people with type 1 diabetes with diabetic nephropathy (in the absence of advanced renal failure) (N=27), found no significant EPO response to lower Hb levels \(^{25}\).

**Level 3**

4.4.3.3 A cross-sectional study conducted in people with diabetes \(^{28}\) found no significant EPO response in anaemic patients (defined as Hb < 12 g/dl for women and Hb <13 g/dl for men) with GFR >60 ml/min/1.73m\(^2\) or > 90 ml/min/1.73m\(^2\).

**Level 3**

4.4.3.4 In a sub-group of iron replete diabetic patients from the above study \(^{28}\), serum EPO levels did not change significantly with Hb level

Table 25:
### Children with chronic renal failure

4.4.3.5 No significant correlation was found between serum EPO and Hb/Hct levels in three studies conducted in children with chronic renal failure (N=7)\(^9\); (N=10)\(^{10}\); (N=37)\(^{11}\).

**Level 3**

4.4.3.6 Likewise, no significant correlation was found between serum EPO levels and renal function assessed by means of eGFR (N=37)\(^{12}\) or SCr (N=30)\(^{13}\) in children with chronic renal failure.

**Level 3**

4.4.3.7 In one study\(^{14}\) Hb and serum EPO levels in children with chronic renal failure and healthy children were as tabulated below.

### Table 26:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hb (g/dL)</th>
<th>Mean serum EPO (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis</td>
<td>30</td>
<td>10.7 ± 2.5</td>
<td>36.2 (range 7 to 235)</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>15</td>
<td>11.6 ± 2.6</td>
<td>39.5 (range 10 to 125)</td>
</tr>
<tr>
<td>Healthy children</td>
<td>20</td>
<td>13.2 ± 0.8</td>
<td>35.2 (range 18 to 64)</td>
</tr>
</tbody>
</table>

**Level 3**
Adults with chronic renal failure on conservative therapy

4.4.3.8 In patients with CKD of varying renal function, CCr 2 to 90 ml/min/1.73m² (N=117), mean serum EPO levels were significantly elevated in all patients when compared to healthy controls (N=59) (P<0.01). In a sub-group analysis, of patients with CCr 2-40 ml/min/1.73m² (N=88), CCr and serum EPO showed a positive correlation (r=0.27, P<0.015) 98.

Level 2+

Unselected population of adults

4.4.3.9 In a random sample of patients investigated by coronary angiography (N=395) stratified by renal function, a significant inverse relationship was found between serum EPO and Hb levels in participants with CCr >40 ml/min (r=-0.35, P<0.0001). No significant correlation was found, however, in participants with CCr <40 ml/min. 100.

Level 3

4.4.4 From Evidence to Recommendations

4.4.4.1 Anaemia is associated with increased EPO levels in individuals without evidence of CKD but the anaemia associated with CKD is characterised by a relative lack of EPO response. However, in the clinical situation routine measurement of EPO levels is of limited value in assessing anaemia.

4.4.4.2 The GDG reached consensus on a threshold GFR of 40 ml/min, below which anaemia is most likely to be of renal aetiology and measurement of erythropoietin levels will not be required except in exceptional circumstances. At GFR levels between 40 and 60 ml/min, the utility of testing is uncertain from the existing evidence, and a research recommendation is given.

4.4.5 Recommendations

4.4.5.1 Measurement of erythropoietin levels for the diagnosis or management of anaemia should not be routinely considered for patients with anaemia of chronic kidney disease. (D(GPP))
5 Management of Anaemia

5.1 Initiation of ESA Therapy in Iron-deficient Patients

5.1.1 Clinical Introduction

5.1.1.1 Iron management forms an essential part of the treatment of anaemia associated with CKD and availability of iron is key for optimal erythropoiesis. Before erythropoietin treatment was available patients with anaemia associated with CKD frequently received blood transfusions. One of the consequences of this was the progressive accumulation of iron, manifested by extremely high ferritin levels in excess of 1500 to 5000 µg/L. With the advent of ESA therapy this accumulated iron was rapidly mobilised, and serum ferritin levels fell accordingly. We now recognise that in order to manage the anaemia optimally there needs to be an appropriate balance between stimulation of erythropoiesis and provision of iron as a key substrate in the manufacture of haemoglobin.

5.1.1.2 In health iron is almost completely recycled and losses are of the order of 1 mg/day, requiring minimal replacement. Iron deficiency anaemia is the most common cause of anaemia world-wide. This is due to either negative iron balance through blood loss (commonly gastrointestinal or menstrual), or to inadequate intake (which may be nutritional or related to poor gastrointestinal absorption). Patients with CKD are particularly susceptible to gastrointestinal blood loss and additional sources of significant blood loss include routine (and non-routine) blood sampling, and blood loss on haemodialysis which may represent the need for up to an extra 3000 mg iron per year. In the first 3 months of ESA therapy it is estimated that a haemodialysis patient needs an extra 1g of supplemental iron, underlining the importance of adequate availability of iron for optimal erythropoiesis 105.

5.1.2 Clinical Methodological Introduction

5.1.2.1 A comprehensive literature search did not identify any studies that were suitable to address the clinical aspects of this section, therefore no evidence statements are given.
5.1.3 Health Economics Methodological Introduction

5.1.3.1 One study met quality criteria. This Canadian study estimated annual cost-savings of intravenous iron dextran from reductions in EPO and oral iron in patients who did not tolerate or did not respond adequately to oral iron in a 6-month prospective study with an initial goal serum ferritin of 100-200 µg/l. If an increase in haemoglobin was not achieved, transferrin saturation was measured and when <20%, the goal serum ferritin was increased to 200-300 µg/l. EPO was used to maintain haemoglobin levels of 9.5-10.5 g/l only if ferritin targets were met.

5.1.4 Health Economic Evidence Statements

5.1.4.1 The study found that intravenous iron dextran (FeD) saved approximately $63 per patient ($3016 total) from EPO savings and oral iron saving in 50 patients. However, the initial cost of IV-FeD loading was $3426 in the first year. Therefore, the loading dose of IV-FeD offsets the cost reduction in EPO and oral iron in the first year but would not apply in subsequent years. Intravenous iron dextran costs were $29,692 (CDN$, 1996) per year in the 50 patients in the study with $30,120 of EPO savings per year and $2738 from oral iron savings per year.

5.1.5 From Evidence to Recommendations

5.1.5.1 There is little evidence in this area but the GDG agreed that ESAs alone should not be administered to patients with iron deficiency (ferritin level < 100 µg/L). The GDG debated whether ESAs should be administered together with iron supplements. It was noted that some patients with higher GFRs had a good response to iron treatment alone but that there was no evidence to support a threshold for iron stores required prior to commencing ESAs, except in patients with iron deficiency.

5.1.6 Recommendations

5.1.6.1 ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency. (D(GPP))

5.1.6.2 In patients with functional iron deficiency, iron supplements should be given concurrently when initiating ESA therapy. (D(GPP))
5.2 Maximum Iron Levels in ACKD Patients

5.2.1 Clinical Introduction

5.2.1.1 Iron is crucial for survival and is necessary for erythropoiesis and the production of usable energy through oxidative phosphorylation. Iron-overload states are harmful and that the potent oxidizing ability of iron makes it a potentially toxic compound in the body in its free form. The majority of iron not actively circulating as haemoglobin is safely sequestered in the form of ferritin and hemosiderin in macrophages of the reticuloendothelial system (RES). Molecules that hold iron tend to be very large, containing a central core of iron with a proteinaceous envelope that insulates the body from the iron atom. We know that in iron-overload states, such as haemochromatosis, in which serum ferritin levels can increase to more than 10,000 µg/L, the body is presented with unmanageable levels of free iron leading to iron-related toxicity. The focus of debate regarding potential iron toxicity in patients with anaemia associated with CKD revolves around the possible increased susceptibility to infectious complications and increased cardiovascular morbidity and mortality engendered by iron administration. In vitro iron preparations enhance bacterial growth, induce leukocyte dysfunction, inhibit phagocytosis, produce reactive oxygen species, increase oxidative stress, consume anti-oxidants and, at very high doses, promote lipid peroxidation and cell death. These observations have led to concern that too much iron might translate these in vitro phenomena into adverse infectious and cardiovascular in vivo effects.

5.2.2 Methodological Introduction

5.2.2.1 A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.
5.2.3 From Evidence to Recommendations

5.2.3.1 Due to the lack of evidence, it was agreed that an upper limit of 800μg/l of ferritin should be used in line with the current European Best Practice Guidelines (Ref). This level is drawn from data on iron toxicity studies performed in the pre-ESA era that demonstrated that high ferritin levels >1000 μg/l led to the deposition of iron in tissues. However, in practice, in order to prevent serum ferritin from rising above 800 μg/l a patient’s iron dose should be reviewed if their serum ferritin levels exceed 500 μg/l. It was noted that it was not known whether there were any long-term consequences related to the administration of intravenous iron as this route by-passed normal absorption routes and homeostatic mechanisms.

5.2.3.2 It should be noted that ferritin is an acute phase protein that is increased during inflammatory events, this affects the interpretation of some of the studies reviewed.

5.2.4 Recommendations

5.2.4.1 In patients treated with iron, serum ferritin levels should not rise above 800μg/l and in order to prevent this the dose of iron should be reviewed when serum ferritin levels reach 500 μg/l. (D (GPP))
5.3 Initiation of ESA Therapy in Iron Replete Patients

5.3.1 Clinical Introduction

5.3.1.1 Patients who are iron replete (ferritin >100 µg/L and %HRC<6% or TSAT ≥20%) yet still have anaemia associated with CKD will not achieve target haemoglobin levels without administration of ESAs. Should all patients regardless of the clinical situation and their functional status receive ESAs? Estimates of the number of people in England and Wales with significant CKD (eGFR< 60 ml/min) and a haemoglobin level below 11 g/dL not currently receiving ESAs suggest that potential number requiring anaemia management are 108,000. However, this estimate was made from an unselected population that will have included those with causes of anaemia other than CKD, a significant number may not have been iron replete, and the mean age of the cohort was 75.1 ± 11.63 years. The National Service Framework for Older People states that “NHS services will be provided, regardless of age, on the basis of clinical need alone”. For many older patients improvement in quality of life is their paramount need, and older people should not necessarily be excluded from these treatments. Becoming able to move around your house independently and therefore not needing admission to a care home would clearly be a successful outcome in treating anaemia.

5.3.1.2 The key goals in the management of anaemia are increased exercise capacity, improved quality of life, improved cognitive function, improved sexual function, reduced transfusion requirements, regression/prevention of left ventricular hypertrophy, improved morbidity, prevention of progression of renal disease, reduced risk of hospitalisation, and reduced mortality. We do not yet have the evidence that all of these goals are achievable but there may be certain patients whose physical and mental status renders these goals unachievable from the outset. Clearly these patients will not therefore benefit from administration of ESAs.

5.3.2 Methodological Introduction

5.3.2.1 A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.
5.3.3 From Evidence to Recommendations

5.3.3.1 The GDG expected there to be a paucity of literature in this area. The reason for investigating the evidence base in this section was to determine whether there were any sub-groups of patients in whom the administration of ESAs may be of little clinical benefit.

5.3.3.2 The GDG discussed whether they considered there were any patient sub-groups with a Hb level below 11g/dL and with stage 3-5 CKD who should not be considered for treatment with ESAs. The GDG felt that it was a matter of clinical judgement, based on a patient's individual circumstances (e.g. presence of co-morbidities), as to whether a patient would benefit from the administration of ESAs.

5.3.3.3 The GDG considered it important to note that antibody mediated Pure Red Cell Aplasia (PRCA) does occur sporadically and this was one group of patients where epoetin administration should be very carefully considered.

5.3.3.4 The GDG felt the most relevant issue was how to best focus resources in the wider CKD population to provide the most benefit. The lack of evidence would suggest this is an area where research is required. The GDG discussed that where there is uncertainty over the benefits that a patient may gain from ESA treatment, a trial of ESA treatment and assessment of response may be indicated prior to continuing long-term treatment. The GDG felt that the patient was as good a judge of whether the treatment had any noticeable improvement on their QOL and did not feel there was any need to recommend any formal tests. The GDG felt strongly that the decision to actively manage an individual patient's anaemia should be made by an experienced clinician, but that this did not necessarily have to be a renal physician.

5.3.4 Recommendations

5.3.4.1 In patients with anaemia of CKD, the pros and cons of a trial of anaemia management should be discussed between the clinician, the patients and carers (if applicable). (D (GPP))

5.3.4.2 In patients with anaemia of CKD, ESAs need not be administered where the presence of co-morbidities, or the prognosis, is likely to negate the benefits of correcting the anaemia. (D (GPP))

5.3.4.3 In patients with anaemia of CKD, a trial of anaemia correction should be initiated where there is uncertainty over whether the presence of co-morbidities, or the
prognosis would negate benefit from correcting the anaemia with ESAs. (D (GPP))

5.3.4.4 In patients with anaemia of CKD, where a trial of anaemia correction has been performed, the effectiveness of the trial should be assessed, and where appropriate, a mutual decision should be agreed between the clinician, patients and carers on whether to stop or continue anaemia management of CKD using ESAs. (D (GPP))

5.3.4.5 All patients started on treatment for anaemia of CKD should be reviewed after an agreed interval in order to decide whether to continue or stop anaemia management using ESAs. (D(GPP))
5.4 Nutritional Supplements

5.4.1 Clinical Introduction

5.4.1.1 Vitamins are essential cofactors that regulate the metabolic pathways from which lipids, proteins and carbohydrates are generated and processed. The uraemic environment is responsible for the development of significant alterations in serum levels, body stores and function of many vitamins.

5.4.1.2 In patients with more advanced CKD (stages 4 and 5) the dietary restrictions imposed for potassium and phosphate inevitably limit the intake of some vitamins from natural sources. More recently dietary counselling has focused more on nutritional support than dietary restrictions with people eating more liberal diets to try and optimise nutritional status. Currently there are no recommendations or guidance as to which population would benefit from vitamin supplementation and in what quantity. Much of our information with regards to supplementation of vitamins comes from studies with small subject numbers, over short periods of time. Many of the studies only address vitamin requirements in the dialysis dependant population excluding predialysis.

5.4.1.3 Reasons to support vitamin supplementation include dietary restrictions, uraemic toxins, drug–nutrient interactions and the dialysis process itself. Water soluble vitamins are lost during both haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). However this may be offset by the altered kinetics caused by renal failure which may result in reduced urinary losses or renal catabolism. The fact that CKD affects the normal absorption, retention and activity of the necessary micronutrients which support all aspects of carbohydrate, protein and lipid metabolism further strengthens the evidence in favour of supplementation.

5.4.1.4 Less is known about the nutritional requirements of fat soluble vitamins in patients with CKD. Studies report anything from subnormal through normal to enhanced levels. In practise supplementation with fat soluble vitamins is not recommended.

5.4.1.5 Data remains incomplete on individual requirements of vitamins, the handling of vitamins in uraemia, the vitamin status of uraemic patients and the effect of vitamin administration.
5.4.1.6 Carnitine is synthesised in the body from two essential amino acids, lysine and methionine whereas glutathione is a peptide containing the amino acids glutamic acid, cysteine and glycine. Carnitine and glutathione have both been implicated in enhancing responsiveness to EPO in CKD patients but there are few studies to date. In practise, this is not done routinely.

5.4.1.7 Although much is known about the prevalence of macronutrient deficiency in renal patients nutritional status in CKD is beyond the scope of this guideline. This section focuses on micronutrient supplementation and its effect on the treatment of anaemia due to CKD.

5.4.2 Methodological Introduction

5.4.2.1 A comprehensive literature search identified eight studies. Of these, two studies addressed vitamin C. A cross-over RCT\[107\] and a non-randomised controlled trial\[108\]. One RCT addressed folic acid\[109\]. Five studies addressed carnitine supplementation, which consisted of three RCTs\[110, 111, 112\], a cross-over RCT\[113\] and a before and after study\[114\].

5.4.2.2 Eleven studies did not meet quality criteria and were thus excluded from the evidence statements. These include four which addressed vitamin C\[115, 116, 117, 118\], one which addressed vitamin E\[119\] one which addressed folate\[120\] and five which addressed carnitine supplementation\[121, 122, 123, 124, 125\].

5.4.2.3 Of note:

- No studies addressing vitamin E or glutathione were found
- The meta-analysis investigating carnitine supplementation\[121\] did not meet quality criteria, hence the studies within it\[111, 112, 110\] were individually appraised
- One study was conducted in children\[114\]
- One study\[107\] was conducted in a pre-selected patient population

5.4.2.4 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section.

5.4.3 Evidence Statements

**Vitamin C**

**Haemodialysis patients**

5.4.3.1 A non-randomised trial (N=52)\[108\] where 100 mg ascorbic acid was administered i.v. three times weekly in one group (N=23) and as an adjunct to ESA and i.v. iron in another, found no significant change in Hb levels from baseline in either group.
after 6 months. In addition, no changes were identified in either group in any of the 8 domains of quality of life assessed using the Short-Form 36 (SF-36) scale.

**Level 2+**

5.4.3.2 In a RCT of cross-over design (N=27)\(^{107}\), where ascorbic acid 1,500 mg/week was administered i.v. for 3 months, Hb (P<0.01 in Group I and P<0.005 in Group II) and TSAT (both Group I and Group II P<0.001) increased, whereas ferritin decreased (P<0.004 in Group I and P<0.001 in Group II) when compared to baseline levels. Epoetin doses, however, remained unchanged in both groups.

**Level 1+**

*Folic acid*

*Haemodialysis patients*

5.4.3.3 Reticulocyte counts (both P<0.05) and Hct levels (both P<0.01) increased from baseline levels in both sets of patients receiving folic acid 5 mg three times a week over 12 months (N=10) and patients whose folic acid supplementation had been stopped over this time period (N=10). Hct levels further increased (both P<0.01) in the 6-month follow-up period after folic acid supplementation had been stopped in both groups of patients. There were no differences, however in response to epoetin between the two groups\(^ {109}\).

**Level 1+**

*Carnitine*

*Haemodialysis patients*

5.4.3.4 No differences were observed in any of the five domains of quality of life as assessed by the Kidney Disease Questionnaire or in overall quality of life, in a RCT of cross-over design (N=16) in which placebo or 20 mg/kg L-carnitine were administered i.v. over a 12 week duration. Similarly no differences were observed in epoetin dose or Hb levels\(^ {113}\).

**Level 1+**

5.4.3.5 No differences were observed in epoetin dose requirement or Hct and reticulocyte counts in a 6 months study investigating the effects of supplementation with 1 g L-carnitine three times a week in elderly patients (N=28), after which patients were followed up for 3 months\(^ {110}\).

**Level 1+**

5.4.3.6 No differences were found when patients treated with epoetin were supplemented with 1 g carnitine three times a week or placebo (N=24) for 6 months and compared in terms of epoetin dose, endogenous epoetin levels or Hct and iron levels\(^ {111}\).

**Level 1+**
5.4.3.7 No significant changes in epoetin dose requirement were observed between patients supplemented with either 5 mg/kg (N=15) or 25 mg/kg (N=5) L-carnitine vs. placebo (N=20) over 8 months. However, a greater reduction in change in epoetin dose was observed in the carnitine treated group (P<0.05) and a higher epoetin resistance index (epoetin dose:Hb ratio) (P<0.02). Additionally, after 4 months, there were significant negative correlations between plasma free carnitine, plasma total carnitine and plasma free carnitine:plasma total carnitine to EPO dose and ERI in both treatment groups 112.

**Level 1+**

*Paediatric haemodialysis and peritoneal dialysis patients*

5.4.3.8 Total carnitine and free carnitine increased significantly from baseline (both P <0.05) after 26 weeks treatment with orally administered L-carnitine 20 mg/kg daily in both haemodialysis (N=8) and peritoneal dialysis patients (N=4), mean age 10.2 years. Acylcarnitine increased only in haemodialysis patients (N=8) after 26 weeks. Despite this, no changes were observed in Hb levels or epoetin dose from baseline in both sets of patients. In addition, no correlation was found between epoetin dose or Hb levels with total carnitine, free carnitine and acylcarnitine levels 114.

**Level 3**

5.4.4 From Evidence to Recommendations

5.4.4.1 It was concluded that there was no evidence to support the use of Vitamin C, folic acid or carnitine supplements in the treatment of anaemia of CKD. There was very little evidence available for the CKD population and no evidence in the pre-dialysis population. It was considered acceptable to extrapolate the conclusions to the pre-dialysis population.

5.4.4.2 With regard to vitamin C, the appraised studies administered very high doses (1500mg/ wk, 1000mg/wk and 100mg/wk). A dose of 50mg/week was considered to be a more appropriate supplement given in clinical practice to renal patients. The biological basis for the administration of vitamin C was related to aiding the mobilisation iron and promoting effective erythropoiesis. The evidence base was small.

5.4.4.3 In clinical practice, patients are normally given folate supplements this is generally for other reasons outside of the correction of anaemia. The studies appraised on Carnitine supplementation gave negative results.

5.4.5 Recommendations
5.4.5.1 Supplements of Vitamin C, folic acid or carnitine should not be routinely administered as adjuvants to the treatment of anaemia of CKD. (A)
5.5 Androgens

5.5.1 Clinical Introduction

5.5.1.1 Interest in the use of androgens as adjunctive treatment in the management of anaemia associated with CKD stems from their use prior to the availability of ESAs. A number of early studies suggested a beneficial effect on renal anaemia by treatment with androgens, although notably one double blind cross-over trial of nandrolone decanoate failed to show a sustained significant effect on haemoglobin level or red cell mass. However, the requirement for parenteral administration and a number of adverse effects such as acne, flushing of skin, hirsutism, changes in voice, masculinisation, amenorrhoea and increasing libido, together with adverse effects related to liver function such as peliosis as well as hepatocellular adenoma and carcinoma, led to the abandonment of their regular use.

5.5.1.2 The mechanism of action of androgens on erythropoiesis is still not completely understood and mechanisms proposed include increased production of endogenous EPO, synergism with EPO, enhanced sensitivity of erythroid precursors to EPO, increased red cell survival, and a direct effect on erythroid precursors. There is therefore a potential role for androgens in enhancing the effectiveness and reducing the dose requirements of available ESAs.

5.5.2 Methodological Introduction

5.5.2.1 A literature search identified eight studies, including two RCTs, three cohort studies and one before and after study.

5.5.2.2 Two studies did not meet quality criteria and were therefore excluded from the evidence statements.

5.5.2.3 The GDG agreed that the following outcomes were priorities:
- Mortality and morbidity
- Improved response to ESAs
- Quality of life
- Hb/Hct level
- ESA dose
- Adverse effects.

5.5.2.4 Of note:
- The studies were investigating:
  1) Epoetin vs. nandrolone
  2) Epoetin vs. epoetin + nandrolone
  3) Epoetin + nandrolone (no control group)
4) Nandrolone alone (no control group) 136)

- Although side effects were noted in some studies 137,136,133, the authors did not attempt to quantify all of these
- The studies were conducted in both male and female patients except for two studies 134, 132, which were conducted solely in male patients.

5.5.3 Evidence Statements

**Hb/Hct levels**

**Haemodialysis patients**

5.5.3.1 In a before and after study conducted in male (N=9) and female (N=8) patients 137, Hb (P=0.001) and Hct (P=0.003) levels increased following adjuvant therapy with epoetin 3,000 U/week s.c. and nandrolone decanoate 100 mg i.m. weekly for 6 months. When stratified into sex of patients, Hb and Hct levels (both P=0.01) were higher only in female patients.

**Level 3**

5.5.3.2 In a cohort study conducted in male (N=67) and female (N=17) patients 136, Hb and Hct levels rose (both P<0.01) following therapy with nandrolone decanoate 200 mg i.m. weekly for 6 months. Although baseline Hb levels were higher in the male patients (P<0.05), the increase with respect to baseline levels was similar in both sexes throughout the study. In order to evaluate the influence of other factors, patients were divided into non-responders (Hb increase <1 g/dl with respect to baseline; N=28), mild responders (Hb increase 1-1.9 g/dl with respect to baseline; N=18), good responders (Hb increase 2-2.9 g/dl with respect to baseline; N=25) and excellent responders (Hb increase >2.9 g/dl with respect to baseline; N=13). Only age was significantly associated with response to androgen therapy (P<0.01). When the cohort was stratified into ages <46 years (N=29), 46-55 years (N=28) and >55 years (N=27), only the latter two groups showed improvement in Hb levels (both P<0.01) following androgen therapy.

**Level 2+**

5.5.3.3 A 6-month cohort study conducted to compare the effect of 200 mg nandrolone decanoate i.m. once weekly in male patients aged over 50 years (N=18) vs. epoetin 6,000 IU a week in male and female patients aged less than 50 years (N=22) found an increase in Hb levels in both groups (both P<0.01), despite a drop in serum ferritin levels in the epoetin treatment group (P<0.01) 135.

**Level 2+**

5.5.3.4 In a cohort study 134 conducted over 12 weeks in male patients treated with epoetin 6,000 U i.v. 3 times a week (N=7) vs. epoetin 6,000 U i.v. 3 times a week and 100 mg nandrolone decanoate i.m. once a week (N=8), Hct values increased in the
group receiving adjuvant therapy (P<0.001) after 12 weeks and no transfusions were required in either group.

**Level 2+**

5.5.3.5 In a RCT conducted in predominantly black male and female patients administered with epoetin 4,500 U per week vs. epoetin 4,500 U per week (N=10; 4 males and 6 females) and nandrolone 100 mg i.m. once a week (N=9; 7 males and 2 females) over 26 weeks found a significant increase in Hct in both treatment groups when compared to baseline values (P=0.003 and P=0.001 respectively). However, the rise in Hct was greater in the epoetin plus androgen group (P=0.012) when compared to epoetin alone 133.

**Level 1+**

*CAPD patients*

5.5.3.6 Hb and Hct levels increased in both treatment groups in a RCT 132 investigating influence of epoetin initiated at 50 U/kg/week and tailored to target Hb of 11-13 g/dl vs. Nandrolone 200 mg i.m. once weekly (both P<0.001) when compared to baseline values. However, these increases in Hb and Hct levels were not significantly different when the treatment groups were compared to each other.

**Level 1+**

*Epoetin dose*

*Haemodialysis patients*

5.5.3.7 In a before and after study conducted in male (N=9) and female (N=8) patients 137, weekly epoetin doses following adjuvant therapy with nandrolone decanoate 100 mg i.m. weekly for 6 months, did not change either in the overall cohort or when stratified into male and female patients.

**Level 3**

5.5.3.8 In a cohort study conducted over 12 weeks in male patients treated with epoetin 6,000 U i.v. 3 times a week (N=7) vs. epoetin 6,000 U i.v. 3 times a week and 100 mg nandrolone deaconate i.m. once a week (N=8), no difference was observed in epoetin dose between the 2 treatment groups 134.

**Level 2+**

*Adverse events—serum triglycerides*

*Haemodialysis patients*

5.5.3.9 In a cohort study conducted in male (N=67) and female (N=17) patients, serum triglycerides increased (P<0.01) after therapy with nandrolone decanoate 200 mg i.m. weekly for 6 months 136.

**Level 2+**
5.5.3.10 A 6-month cohort study conducted to compare the effect of 200 mg nandrolone deaconate i.m. once weekly in male patients aged over 50 years (N=18) vs. epoetin 6,000 IU a week in male and female patients aged less than 50 years (N=22) found an increase in serum triglycerides in the androgen group (P<0.001).

Level 2+

5.5.4 From Evidence to Recommendations

5.5.4.1 The rationale for the administration of androgens to patients with anaemia of CKD was historical in that androgens were administered in the pre-EPO era. The studies had administered nandrolone decanoate but this androgen is no longer used in clinical practice. The doses of nandrolone administered in the studies were considered to be supraphysiological. The group agreed that there was some evidence of efficacy that the administration of androgens could reduce the dose of ESA required but were concerned about the potential side effects and considered this an out-dated approach to anaemia management.

5.5.5 Recommendation

5.5.5.1 In patients with anaemia of CKD, androgens should not be used to treat the anaemia. (C)
5.6 Hyperparathyroidism

5.6.1 Clinical Introduction

5.6.1.1 Elevations in serum parathyroid hormone (PTH) concentration (secondary hyperparathyroidism) are seen early in CKD and are common when the estimated GFR is < 60 ml/min (stage 3 CKD onwards)\textsuperscript{140-142}. Elevation of PTH in the CKD 3 and 4 populations predicts the development of more severe hyperparathyroidism, which in turn is clearly associated with increased skeletal and cardiovascular morbidity and mortality\textsuperscript{143}. Whether hyperparathyroidism causes anaemia and resistance to treatment of anaemia, and if it does what degree of hyperparathyroidism is clinically important, remain controversial. Potential mechanisms include a direct effect of PTH on endogenous EPO synthesis, on bone marrow erythroid progenitors, and on red cell survival through accelerated haemolysis; and an indirect effect through induction of bone marrow fibrosis. This section looks at whether treatment of hyperparathyroidism in people with anaemia associated with CKD improves the management of anaemia in terms of haemoglobin level achieved and dose of ESA required; and also attempts to determine when treatment should be considered.

5.6.2 Methodological Introduction

5.6.2.1 A literature search identified seven studies. These consisted of a cohort study\textsuperscript{144}, a 2-part study comprised of a cohort study and prospective before and after study\textsuperscript{145}, a 2-part study comprised of prospective longitudinal study and cohort study\textsuperscript{146}, a prospective before and after study and a cohort study\textsuperscript{147}, a prospective longitudinal study\textsuperscript{148}, and two retrospective before and after studies\textsuperscript{149, 150}.

5.6.2.2 Six studies\textsuperscript{151, 152, 153, 154, 155, 156} did not meet quality criteria and were therefore excluded from the evidence statements.

5.6.2.3 The GDG agreed that the following outcomes were priorities:
- Parathyroid hormone levels
- Mortality and morbidity
- Quality of life
- ESA dose
- Improved response to ESA
- Plasma erythropoietin levels
- Reduction in ESA resistance
- Hb/Hct level

5.6.2.4 Of note:
• Treatment for parathyroidism was stratified into drug-based with calcitriol\textsuperscript{145,146}, alfalcaldol\textsuperscript{148} or surgery\textsuperscript{150,145,149,144,144}

5.6.2.5 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.
### 5.6.3 Evidence Statements

Table 27: summary of evidence for appraised studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug-based therapy</th>
<th>Sample size</th>
<th>Baseline iPTH levels (pg/ml)</th>
<th>Treatment duration</th>
<th>Outcome</th>
<th>Effect</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>Calcitriol 2g</td>
<td>N=16</td>
<td>778 ± 172.7</td>
<td>6 months</td>
<td>N=7 responders</td>
<td>↓ ↑ ↓</td>
<td>Level 2+</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>iPTH</td>
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<td>Hct</td>
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<td></td>
<td></td>
<td>Epoetin dose</td>
<td></td>
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</tr>
<tr>
<td>146</td>
<td>Alfacalcidol 6 mg</td>
<td>N=12</td>
<td>~475</td>
<td>18 months</td>
<td>iPTH</td>
<td>↓ ↑ ↓</td>
<td>Level 3</td>
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<td></td>
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<td></td>
<td>Hb</td>
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<tr>
<td>146</td>
<td>Calcitriol i.v. 2 µg</td>
<td>N=28</td>
<td>811.6 ± 327</td>
<td>12 months</td>
<td>Hb/Hct</td>
<td>↑ ↓ ↓</td>
<td>Level 3</td>
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<tr>
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<td>iPTH</td>
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<tr>
<td>146</td>
<td>Calcitriol i.v. 2 µg</td>
<td>N=28</td>
<td>811.6 ± 327</td>
<td>12 months</td>
<td>Epoetin use (N=21) vs. No Epoetin (N=7)</td>
<td>No change</td>
<td>Level 2+</td>
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<td></td>
<td>Epoetin dose</td>
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<tr>
<td>146</td>
<td>Calcitriol i.v. 2 µg</td>
<td>N=28</td>
<td>811.6 ± 327</td>
<td>12 months</td>
<td>Responders (N=19) vs. non-responders (N=9)</td>
<td>↑ No change</td>
<td>Level 2+</td>
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<td>Hct</td>
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<td>Epoetin dose</td>
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<tr>
<td>Procedure</td>
<td>N</td>
<td>Pre-surgery Hct</td>
<td>Hb</td>
<td>Post-surgery Hct</td>
<td>Hct</td>
<td>Epoetin dose</td>
<td>Level</td>
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</tr>
<tr>
<td>Subtotal parathyroidectomy (N=9) and total parathyroidectomy with forearm autotransplantation (N=1)</td>
<td>10</td>
<td>Not reported</td>
<td></td>
<td>6 months</td>
<td>↓</td>
<td>↑ ↓</td>
<td>Level 3</td>
</tr>
<tr>
<td>Total parathyroidectomy with forearm autotransplantation (N=3)</td>
<td>3</td>
<td>976 ± 436.1</td>
<td></td>
<td>6 months</td>
<td>↓</td>
<td>↑ ↓</td>
<td>Level 3+</td>
</tr>
<tr>
<td>Subtotal parathyroidectomy</td>
<td>19</td>
<td>1,726 ± 1,347</td>
<td></td>
<td>1-2 years (N=44)</td>
<td>↑</td>
<td>No change</td>
<td>Level 3</td>
</tr>
<tr>
<td>Total parathyroidectomy and autotransplantation</td>
<td>10</td>
<td>913 ± 380</td>
<td></td>
<td>3-5 years (N=24)</td>
<td></td>
<td>↑</td>
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<tr>
<td>Total parathyroidectomy</td>
<td>10</td>
<td>1,006 ± 668</td>
<td></td>
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<tr>
<td>Partial parathyroidectomy (removal of 2-3 parathyroid glands)</td>
<td>6</td>
<td>1,176 ± 3346</td>
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</tbody>
</table>
| Total parathyroidectomy and forearm autotransplantation | N=29 | 873 ± 710.8 | 12 months | iPTH | Hb | Plasma erythropoietin | Epoetin use (N=23) vs. No Epoetin (N=6) | Epoetin dose | No change | ↓↑↑ | Level 3
<table>
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<tbody>
<tr>
<td>N.B. N=7 underwent reoperation for recurrences in neck and forearm</td>
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</table>

| Total parathyroidectomy and forearm autotransplantation | N=32 | Responders 1,338 ± 350.6 | 3 months | N=17 responders (≥10% Hb increase post-PTX) vs. N=15 non-responders | Hb | Serum erythropoietin | iPTH | No change | No difference | ↓ but no difference between the 2 groups | Level 2+
<table>
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<tr>
<td>N=17 responders (≥10% Hb increase post-PTX) vs. N=15 non-responders</td>
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</tbody>
</table>

↓↑ = significant increase
↓ = significant decrease

PTX = parathyroidectomy
5.6.4 From Evidence to Recommendations


5.6.5 Recommendation

5.6.5.1 In patients with anaemia of CKD, clinically relevant hyperparathyroidism should be treated to improve the management of the anaemia. (C)
5.7 Patient-Centred Care: ESAs

5.7.1 Clinical Introduction

5.7.1.1 The ESAs currently available in clinical practice differ in terms of frequency of administration and route of administration. Darbepoetin and erythropoetin beta may be administered either subcutaneously or intravenously, erythropoetin alpha is currently only licensed for intravenous usage. Darbepoetin is likely to require less frequent administration than the erythropoietins and erythropoetin beta is likely to require less frequent administration and a lower dose when administered subcutaneously versus intravenously. Logistically it is easier for patients not on haemodialysis to receive ESAs subcutaneously by self-administration or administration by their carer/practice nurse at home; patients on haemodialysis may also elect to receive their ESA either through self-administration or from dialysis staff at the end of haemodialysis.

5.7.1.2 Key considerations for patients with anaemia associated with kidney disease are firstly that ESAs are prescribed when clinically indicated; secondly that the ESA supply, route of supply and storage arrangements are clearly defined, secure and convenient; and thirdly that the administration and monitoring of anaemia treatment is as efficient, comfortable and least disruptive as possible.

5.7.2 Methodological Introduction

5.7.2.1 Seven studies were identified, including two RCTs; one of which was of cross-over design; one retrospective longitudinal study; one retrospective case series and three cross-sectional studies. One study did not meet quality criteria and was thus excluded from the evidence statements.

5.7.2.2 Of note:

- The studies conducted using questionnaires were limited by the use of closed questions in their design, with the exception of one study, which reported the use of both closed and open questions.
- All the studies using questionnaires were cross-sectional, with the exception of one study, which was of longitudinal design.
5.7.2.4 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.

5.7.3 Evidence Statements

Route of administration—effect on quality of life
Haemodialysis patients

5.7.3.1 In a 24-week cross-over study\textsuperscript{157} where s.c. was compared to i.v. administration, quality of life assessed by means of the Kidney Disease Questionnaire (KDQ), which consists of 5 domains, found improvements from epoetin administration (both intravenous and subcutaneous) in the physical (P<0.05) and fatigue (P<0.05) domains, but no differences between the two modes of administration in any quality of life scores.

Level 1+

Differences in ESA preparations—effect on pain
Haemodialysis patients

5.7.3.2 A 2-week study\textsuperscript{158} investigating the differences between two epoetin preparations by means of a standardised Visual Analogue Scale (VAS) and a Verbal Descriptive Scale (VDS) found that epoetin alfa was more painful than epoetin beta. The latter was also found to be less painful than placebo injections.

Level 1+

Adherence and ESA administration
Peritoneal dialysis patients

5.7.3.3 In a retrospective longitudinal study\textsuperscript{159}, 19 of 54 (35 %) patients administering s.c. epoetin in the home setting were non-concordant (defined as less than 90% of the prescribed dose used), with the most reported reason being forgetfulness. Missing dialysis exchanges, completion of secondary education and younger age were found to be independent predictors of non-adherence ($r^2=0.36$).

Level 3

5.7.3.4 In a retrospective study\textsuperscript{160}, 30 of 55 (55%) patients administering epoetin s.c. in the home setting were non-concordant (defined as less than 90% of the prescribed dose used). Whether another person administered the EPO on behalf of the patient was the only significant correlation with concordance ($r=0.46$, $P=0.005$).

Level 3
5.7.3.5 Concordance ranged from 24-33%, with the over 60-years of age group least likely to miss an EPO dose and reduced frequency of administration associated with less missed doses. The majority of patients were likely to self-administer. 72.5% preferred fewer injections, with the under 60-years old group preferring once-weekly due to convenience, pain on injection and epoetin storage.

5.7.3.6 57 of 86 (66%) patients reported they never missed doses, whilst 31% admitted to occasionally missing doses and 3% admitted to frequently missing doses. Following a missed dose, the majority (39%) informed the renal unit, 27% carried on as usual after the missed dose, 19% administered the missed dose as soon as they remembered. The majority (55%) of patients preferred self-administration of epoetin, with 17% reporting difficulties with injection preparation and 17% reporting pain at the injection site.

5.7.3.7 The majority of patients (89%) reported the renal unit anaemia nurse to be the preferred source of information. However, most patients (59%) reported they did not need more information. Most requests for information were found to be about how epoetin works (31%), possible side effects (29%) and what epoetin is for (26%). Epoetin supply was found to be mostly by GPs (71%), although 20 patients (23%) reported that their GPs had refused to supply epoetin. Most patients preferred obtaining epoetin supplies from community pharmacy (N=63).

5.7.3.8 Most (91%) anaemic patients received epoetin therapy. Of the 4% that were refused epoetin, the reasons given were that the GP could not pay for it (50%) and that the hospital could not pay for it (20%).
EPO administration—effect on quality of life
Pre-dialysis, dialysis and transplant patients

5.7.3.9 Sleep disturbance, tiredness and ability to attend a 9am to 5pm job were found to be associated with baseline Hb and post-treatment levels. Patients whose post-treatment Hb levels had increased from below 11 g/dl to above 11 g/dl were 1.8 times more likely to report an improvement in QoL. Patients with post-treatment Hb levels >11 g/dl were 1.9 times more likely to agree with the statement “I can attend a 9am-5pm job” 163.

Level 3

5.7.4 From Evidence to Recommendations

5.7.4.1 The evidence from seven studies contained outcome data on QOL, pain, concordance, obtaining EPO and communication with patients.

5.7.4.2 The data supported the view that patient preferences and experiences should be taken into account, where possible, when decisions are reached regarding treatment with ESAs. The patient should be given access to sufficient information about their condition and its treatment to allow them to make informed choices about the management of their condition (e.g. whether to have supervised- or self-administration of ESAs). It was noted that some studies had shown an increased lack of concordance in some groups who had chosen self-administration [244; 1651]. Patients need to be aware of the consequences of poor concordance and one study highlighted that a reduced frequency of administration of ESAs resulted in increased concordance 161. Currently many patients have difficulties securing a supply of ESAs. Many patients are unable to obtain ESAs from their local hospital or GP practice and have the ESAs delivered to them at home. This can cause problems in finding the capacity to refrigerate large quantities of drugs. This area needs to be addressed by health care providers to allow adequate drug supply and storage facilities for patients.

5.7.5 Recommendations

5.7.5.1 Both patients offered ESA therapy and their GPs should be given information about why ESA therapy is required, how it works, and what benefits and side effects they may experience. (D)

5.7.5.2 When managing patients with anaemia of CKD, there should be agreed protocols defining roles and responsibilities of professionals in primary and secondary care. (D(GPP))
5.7.5.3 Patients should have a designated contact person for their anaemia management. (D(GPP))

5.7.5.4 Patients receiving ESA therapy should be informed about the importance of concordance with therapy and the consequences of poor concordance. (D)

5.7.5.5 When prescribing ESA therapy considerations should be given to patient preferences about supervised- or self-administration, dose frequency, pain on injection, method of supplying ESA and storage. (D)

5.7.5.6 In order for patients 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. (D)
5.8 Patient Education Programmes

5.8.1 Clinical Introduction

5.8.1.1 Patient self-management is one of the cornerstones of chronic disease management, enabling patients some degree of control of their own disease process. The level of independence each individual achieves depends as much on the quality of the information and self-management tools provided as it does on the ability of the individual patient. Patient education programmes are therefore of paramount importance in achieving effective patient self-management.

5.8.1.2 Structured patient education involves planned education that covers all aspects of anaemia management and is flexible in content, is relevant to a person’s clinical and psychological needs, and is adaptable to their educational and cultural background. A well planned education course will provide a written outline, be delivered by trained educators (preferably someone who is both well versed in the principles of patient education and is competent to teach the programme), be quality assured, and provide the opportunity for feedback.

5.8.2 Methodological Introduction

5.8.2.1 A comprehensive literature search did not identify any clinical or health economic studies that were suitable to address this section.

5.8.3 From Evidence to Recommendations

5.8.3.1 Patient education was considered to be hugely important and information should be available at different levels. Adequate information helps patients to make decisions about their treatment and illness, although it was noted that there might be some patients who will wish to remain passive about their condition.

5.8.3.2 Patient education should meet the individual needs of each patient and five themes were considered to be important:

- Practical management of anaemia
- Knowledge (about symptoms, iron and ESA management & product delivery and storage)
• Professional support (contact information, community services, continuity of care, monitoring, feedback on progress of results)
• Lifestyle (diet, physical exercise, maintaining normality, meeting other patients)
• Adaptation (causes of anaemia, associated medications, phases of treatment, previous information and expectations, resolution of symptoms)

5.8.4 Recommendations

5.8.3.3 Culturally and age-appropriate patient education programmes should be offered to all patients (and carers) diagnosed with anaemia of CKD and repeated as requested, and according to the changing circumstances of the patient. This should encompass understanding of the following key areas: (D(GPP))
- Practical information about how anaemia of CKD is managed
- Knowledge (e.g. about symptoms, iron management, causes of anaemia, associated medications, phases of treatment)
- Professional support (e.g. contact information, community services, continuity of care, monitoring, feedback on progress of results)
- Lifestyle (e.g. diet, physical exercise, maintaining normality, meeting other patients)
- Adaptation to chronic disease (e.g., previous information and expectations, resolution of symptoms)
6 Assessment and Optimisation of Erythropoiesis

6.1 Benefits of Treatment with ESAs

6.1.1 Clinical Introduction

6.1.1.1 The introduction of ESAs into clinical practice nearly 20 years ago dramatically changed the management of anaemia associated with chronic kidney disease. Prior to ESA therapy dialysis-dependent patients were profoundly anaemic, frequently manifesting haemoglobin levels of between 6 -7 g/dL, the only treatments available being blood transfusions, iron or androgen therapy. The potential benefits associated with anaemia treatment are numerous. These include avoidance of blood transfusions with their attendant risks of sensitisation against future transplantation, iron overload, blood-borne disease and transfusion reactions; improved quality of life and physical functioning; improved cognitive and sexual function; cardiovascular benefits in terms of structure, function, incidence and prevalence of disease; and reduced hospitalisation, morbidity and mortality.

6.1.2 Clinical Methodological Introduction

6.1.2.1 Four studies were identified. A meta-analysis (epoetin vs. placebo or no treatment)\(^{165}\), two multisite RCTs (epoetin vs. placebo)\(^{166,167}\), one cohort study (epoetin vs. no treatment)\(^{168}\) and a retrospective longitudinal study\(^ {169}\). Two studies\(^ {169,170}\) had methodological limitations and were therefore excluded.

6.1.2.2 The outcomes to assess the efficacy of the ESA preparations in comparison to placebo or no treatment were morbidity, left ventricular hypertrophy, left ventricular function, mortality, hospitalisation and dialysis adequacy.

6.1.2.3 Of note:

- All studies except for two included in the meta-analysis\(^ {165}\) did not explicitly state if they used epoetin \(\alpha\) or epoetin \(\beta\)
- The study durations ranged from 12 weeks to 3.5 years
- Studies included in the meta-analysis\(^ {165}\) achieved a lower Hb level and excluded patients with significant comorbidities
- In one study\(^ {167}\) red cell transfusions were given to placebo or treatment arms when required

6.1.3 Clinical Evidence Statements

Quality of Life
Predialysis Patients
Studies in the meta-analysis\(^ {165}\)
6.1.3.1 Kleinman, 1989, by means of a visual analogue scale rating of three questions, found an improvement in quality of life after 12 weeks with a mean difference of 35 (95% CI 12.47 to 57.53). Roth, 1994, by means of the Sickness Impact Profile and other validated tests, found an improvement at 48 weeks, with the control group having decreased physical function (P=0.03) and the epoetin group having increased physical function (P=0.015) as well as increase in energy (P=0.045). However, the number of domains assessed in this study were not provided by the authors.

Level 1+

Haemodialysis Patients

6.1.3.2 In one study 171, an improvement in four out of five categories of the Kidney Disease Questionnaire were found (physical P<0.001; fatigue P<0.001; relationships P=0.001; depression P=0.018). In addition, the Sickness Impact Profile questionnaire found an improvement in quality of life as reflected by the reduction of the global scores (P=0.024) and the physical scores (P=0.005). Psychosocial scores were non significant.

Level 1+

Mortality

6.1.3.3 There was insufficient mortality data available from the meta-analysis 165 and the RCT 167 to write evidence statements.

Hospitalisation

Study participants new haemodialysis patients

6.1.3.4 No statistically significant difference in hospitalisation between epoetin and placebo treatment groups was found, including when stratified and analysed into admission type, age group and history of cardiovascular disease 168.

Level 2+

6.1.4 Health Economics Methodological Introduction

6.1.4.1 Three studies were identified [5 /id];172;[272 /id]. One study 173 did not meet met quality criteria and therefore no evidence statements were made.

6.1.4.2 One study contained a cost-effectiveness analysis before and during epoetin therapy [5 /id]. It was predominantly a cost-savings analysis with 1990-1991 UK£ and earlier costs. However, the 1990-1991 or earlier cost data meant that there was insufficient data from which to derive evidence statements for application to the current NHS context.
6.1.4.3 One study compared cost/QALY results in 5 European countries including the UK. This study used QALYs as the effectiveness measure. Nevertheless, cost data was derived from 1988 values, which indicates there is insufficient data from which to derive evidence statements for the current NHS context.

6.1.4.4 An additional study evaluated the cost per QALY of epoetin using the same framework as the Leese study (1988 values), but updated data with values from the year 2000 in the UK.

6.1.5 Health Economics Evidence Statements

6.1.5.1 The cost per QALY of EPO treatment in the UK using data from the year 2000 was £17,067. The model was most sensitive to changes in the QALY gain. The baseline QALY gain used to derive the cost per QALY was 0.088 per year. However, if a 0.17 QALY gain occurs, the cost per QALY drops to £8,809, conversely if a 0.02 QALY gain occurs, the cost per QALY would increase to £74,876.

6.1.6 From Evidence to Recommendations

6.1.6.1 One study was appraised that assessed mortality but the GDG considered the study to be underpowered to determine whether there was a clinically important difference in mortality rate. The GDG felt that the data was not sufficient to make a sound evidence statement.

6.1.6.2 The GDG concluded that the study of people receiving peritoneal dialysis did not contribute meaningful data as the study duration was considered too short (12 weeks) to effectively assess mortality.

6.1.6.3 Of the outcomes assessed the GDG felt there was only good evidence supporting improvement in quality of life through ESA treatment. The GDG noted that the studies had small sample sizes and had concerns over the statistical validity of the evidence. The studies in the meta-analysis achieved a low target haemoglobin and the patients that may have shown the greatest benefits were excluded from the studies.

6.1.6.4 The GDG noted that because highly selected populations were included in these studies the effects reported were not as large as those observed in the unselected patients populations observed in clinical practice.

6.1.6.5 The GDG concluded that on the basis of qualitative data and clinical experience that ESAs are of value.
6.1.6.6 Health economic data was presented to the group. The GDG agreed that one study was presented that was sufficiently robust to be included and gave useful cost per QALY information in the UK context. However, as the model was sensitive to the gain in QALY, the GDG felt further economic evidence is required before definitive statements about the cost-effectiveness are made. The GDG felt the other studies:

- Estimated the price but under-estimated the benefit of the treatment (n= 24)
- Were based on a study design that could introduce bias, or
- Were based on historical cost data that no longer had relevance to the current NHS context.

6.1.7 Recommendations

6.1.7.1 Patients with anaemia of CKD who are likely to benefit from ESAs in terms of quality of life and physical function should be offered treatment. (A)

See 3.2.3 for the associated algorithm.

6.2 Blood Transfusions

6.2.1 Clinical Introduction

6.2.1.1 The potential risks of blood transfusion include transfusion reactions, immunomodulation, iron overload and transfusion transmitted infections.

6.2.1.2 Data concerning adverse transfusion events in the UK is collected by the Serious Hazards of Transfusion (SHOT) group. Their 2003 report included data from 351/415 UK hospitals (see www.shotuk.org). Since the inception of SHOT in 1996 there has been a year-on-year increase in the number of adverse transfusion incidents reported with now over 2000 recorded in the SHOT database (Table X). Although the numbers of transfusion transmitted infections reported are low, the list of infections that may be potentially transmitted is growing rapidly and includes Hepatitis B, C & G, Human Immunodeficiency Virus (HIV), Human T-Lymphocytotropic Virus (HTLV-1), Transfusion Transmitted Virus (TTV), Cytomegalovirus (CMV), Creutzfeld-Jakob Disease (CJD), Human Herpes Virus (HHV-8), Leishmaniasis, Lyme Disease, Malaria, Babesiosis and Toxoplasmosis.

Table 28. 2003 Serious Hazards of Transfusion (SHOT) Report

<table>
<thead>
<tr>
<th>SHOT Category</th>
<th>Reported Cases 1996-2003, n (%)</th>
<th>Risk Category</th>
<th>Estimated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect blood component transfused</td>
<td>1393 (66.7)</td>
<td>Risk of Incorrect blood component transfused</td>
<td>1 in 16,500</td>
</tr>
<tr>
<td>Acute transfusion reaction</td>
<td>233 (11.2)</td>
<td>Risk of ABO incompatible</td>
<td>1 in 102,200</td>
</tr>
</tbody>
</table>
### Delayed transfusion reaction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk</th>
<th>Risk (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed transfusion reaction</td>
<td>213</td>
<td>(10.2)</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury</td>
<td>139</td>
<td>(6.7)</td>
</tr>
<tr>
<td>Risk of Transfusion-related acute lung injury</td>
<td></td>
<td>1 in 165,000</td>
</tr>
<tr>
<td>Transfusion-transmitted infection</td>
<td>45</td>
<td>(2.2)</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>44</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Risk of serious hazard</td>
<td></td>
<td>1 in 11,000</td>
</tr>
<tr>
<td>Transfusion-associated GVHD</td>
<td>13</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Risk of major morbidity</td>
<td></td>
<td>1 in 92,000</td>
</tr>
<tr>
<td>Unclassified</td>
<td>7</td>
<td>(0.3)</td>
</tr>
<tr>
<td>Risk of death</td>
<td></td>
<td>1 in 255,500</td>
</tr>
</tbody>
</table>

### 6.2.1.3 Prior to the introduction of ESAs,

...the two biggest concerns for patients with CKD were sensitisation against future transplantation and iron overload. This was complicated by the evidence suggesting that transfusion prior to transplantation may actually be beneficial in terms of future transplant outcome. This had been first suggested in 1973. However, a subsequent assessment following the introduction of cyclosporine failed to confirm a benefit and this subject remains controversial. Donor specific transfusion prior to living related transplantation appears favourable but in cadaveric transplantation the picture is less clear. A multicentre randomised controlled trial of transfusion of three units of packed cells demonstrated improved graft survival at one and five years. However approximately 5% of the patients in this study became sensitised, and had not been transplanted by the end of the study period. In children a retrospective study hinted at a beneficial effect from transfusion of 1-5 units of blood, but this beneficial effect was lost with greater numbers of units transfused. A recent study looking at the causes of sensitisation of potential renal allograft recipients in Ireland in the post-EPO era demonstrated that the level of sensitisation clearly increased with the number of units transfused. Non-sensitised participants received a mean of 5.65 units (SEM 1.38), sensitised participants (PRA<10%) a mean of 9.8 units (SEM 3.17), significantly sensitised (PRA 60-79%) a mean of 18.2 units (SEM 6.51), while highly sensitised participants (PRA ≥80%) received a mean of 37.8 units (SEM 8.4). There was a direct relationship between the waiting time for transplantation and the degree of sensitisation.

### 6.2.1.4 Although blood transfusion is not the only factor related to recipient sensitisation,

...since ESAs have become more freely available and the use of routine blood transfusion for correction of anaemia has disappeared, sensitisation has markedly reduced.
6.2.2 Methodological Introduction

6.2.2.1 A comprehensive literature search identified two studies, which consisted of a case-control study \(^{181}\) and a before and after study \(^{182}\).

6.2.2.2 Five studies \(^{183,184,185,186,180}\) did not meet quality criteria and were therefore excluded from the evidence statements.

6.2.2.3 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

6.2.3 Evidence Statements

**Immunological parameters / sensitisation**

**Haemodialysis patients**

6.2.3.1 No significant differences were observed in the analyses of lymphocytes, monocytes, T8, T4, T11, T13, Ia and B1 cells or T4/T8 ratios in patients who had previously received five or more transfusions over 6 months (N=30) when compared with a matched lightly transfused group (N=30) \(^{181}\).

*Level 2+*
Dialysis patients

6.2.3.2 More patients in the lightly transfused group developed narrowly reactive antibodies (reacting with 10-29% panel cells) in comparison to the more heavily transfused group who developed antibodies against ≥30% panel cells. Sensitisation increased waiting time for transplants both in subsequently transplanted patients (P<0.003) and the entire patient population regardless of transplantation (P<0.03) \(^{182}\).

Level 3

6.2.4 From Evidence to Recommendations

6.2.4.1 The GDG noted the lack of evidence on important factors that would impact on the risks of correcting anaemia with regular blood transfusions, such as blood borne viruses and iron overload. In the late 1970s and early 1980s there was evidence that giving blood transfusions before transplantation improved transplant outcome and most units had a deliberate transfusion policy; most research focused on the risks of sensitisation which meant that certain donors would be excluded if the antibodies were directed to their lymphocytes (detected in the "cross match test"). Around the mid 1980s transmission of blood borne viruses by transfusion (in particular HIV) became a major public health issue. At the same time cyclosporin came into regular use. Cyclosporin improved survival, and taken together with the risk of the transmission of blood borne viruses and the availability of epoetin for treating anaemia, deliberate transfusion was discontinued.

6.2.4.2 The GDG considered the evidence on the immunological risks of correcting anaemia with regular blood transfusions. They agreed that the evidence relating to the development of cytotoxic antibodies to lymphocytes \(^{182}\) was more clinically relevant than the data on the levels of different subtypes of lymphocytes induced by transfusion \(^{181}\). It was noted that the blood transfusion increased the percentage of cytotoxic antibodies in dialysis patients resulting in not only an increased waiting time for a transplant but also increased difficulty in finding a cross match negative donor.

6.2.4.3 The GDG felt it was important to stress the benefits of transfusion when clinically indicated for blood loss or in some cases the correction of anaemia (e.g. in some elderly patients). The GDG agreed that there were general clinical reasons to avoid blood transfusion and the relevant haematology guidelines should be reviewed (e.g. The British Committee for Standards in Haematology (BCSH) guidelines http://www.bcsghguidelines.com).
6.2.5 Recommendations

6.2.5.1 In patients with anaemia of CKD, in whom kidney transplant is a treatment option, blood transfusions should be avoided where possible. (D)

6.2.5.2 In patients with anaemia of CKD there may be situations where a transfusion is indicated clinically, and in this case, the relevant haematology guidelines should be adopted. (D (GPP))

6.3 Comparison of ESAs

6.3.1 Clinical Introduction

6.3.1.1 Erythropoiesis stimulating agents (ESAs) are agents stimulating production of red blood cells through a direct or indirect action on erythropoietin receptors of erythroid progenitor cells in the bone marrow. There are 3 licensed forms of ESA currently available in England and Wales, two short-acting (epoetin alfa and epoetin beta) and one long-acting (Darbepoetin alfa).

6.3.1.2 Epoetin alfa (EPO\(\alpha\)) is a glycoprotein manufactured by recombinant DNA technology and has the same biological effects as endogenous erythropoietin. It has an apparent molecular weight of 32,000 to 40,000 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The protein fraction of the molecule contributes about 58% and consists of 165 amino acids. Four carbohydrate chains are attached via three N-glycosidic bonds and one O-glycosidic bond to the protein moiety. EPO\(\alpha\) obtained by gene technology is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

6.3.1.3 In both patients and normal volunteers, after IV administration of EPO\(\alpha\), serum levels decline in a monoexponential manner and the volume of distribution is similar to that of the plasma volume. The t1/2 in normal volunteers is approximately 5 hours, but in patients with renal failure it is prolonged to approximately 9 hours. With multiple injections of EPO, t1/2 and clearance decrease. Measurement of EPO\(\alpha\) following multiple dose intravenous administration revealed a half-life of approximately 4 hours in normal volunteers and approximately 5 hours in renal failure patients. A half-life of approximately 6 hours has been reported in children. Although not currently licensed for subcutaneous use, after SC administration of EPO\(\alpha\) peak serum levels occur between 12 and 18 hours postdose. The peak is always well below the peak
achieved using the IV route (approximately 1/20th of the value). The bioavailability of subcutaneous injectable EP0α is approximately 20% lower than that of the intravenous drug. Elevated levels of EP0α are found in the serum at 48 h after a subcutaneous dose, but not after an IV dose.

6.3.1.4 Epoetin beta (EPOβ) is also identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anaemic patients. Pharmacokinetic investigations in healthy volunteers and uraemic patients show that the half-life of intravenously administered epoetin beta is between 4 and 12 hours and that the distribution volume corresponds to one to two times the plasma volume. After subcutaneous administration of EPOβ to uraemic patients, the protracted absorption results in a serum concentration plateau, whereby the maximum concentration is reached after an average of 12 – 28 hours. The terminal half-life is higher than after intravenous administration, with an average of 13 – 28 hours. The bioavailability of EPOβ after subcutaneous administration is between 23 and 42 % as compared with intravenous administration.

6.3.1.5 The biological efficacy of EPOα and EPOβ have been demonstrated in various animal models in vivo (normal and anaemic rats, polycythaemic mice). After administration of EPOα and EPOβ, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the ⁵⁹Fe-incorporation rate. It has been shown in cell cultures of human bone marrow cells that EPOα and EPOβ stimulate erythropoiesis specifically and do not affect leucopoiesis.

6.3.1.6 Darbepoetin alfa is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. It is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains. The two additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone.

6.3.1.7 Darbepoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin as EPOα and EPOβ. Following SC administration, absorption is slow and rate limiting. The observed half-life in patients with renal failure was 49 hours (range: 27 to 89 hours) and reflects the rate of absorption. Following IV administration to patients with renal failure serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life of 21 hours. Following SC administration in patients with renal failure peak concentrations occur at 34 hours (range: 24 to 72 hours). Following IV administration, the terminal half-life of Darbepoetin is approximately 3-fold longer than EPOα. The bioavailability of Darbepoetin in patients with renal failure after SC administration is 37% (range: 30% to 50%).
6.3.1.8 Darbepoetin and EPOβ are both licensed for intravenous and subcutaneous use, EPOα is currently only licensed for intravenous use.

### 6.3.2 Clinical Methodological Introduction

**Epoetin α vs. Epoetin β**

6.3.2.1 There were no studies comparing epoetin α and epoetin β.

**Darbepoetin vs. Epoetin α**

6.3.2.2 One multisite RCT \(^{187}\) comparing darbepoetin and epoetin α was identified. One study \(^{188}\) was excluded due to methodological limitations.

6.3.2.3 Of note:

- Of the 28 week study duration \(^{187}\), the first 20 weeks were a dose titration and stabilisation period

**Darbepoetin vs. Epoetin β**

6.3.2.4 A comprehensive literature search identified one open-label RCT comparing darbepoetin and epoetin beta \(^{189}\).

6.3.2.5 Of note:

- Darbepoetin dose was converted at 200IU:1µg according to the manufacturer’s dose conversion

6.3.2.6 The GDG agreed that the following outcomes were priorities in assessing the efficacy of the ESA preparations:

- Haemoglobin level
- ESA dose
- Morbidity
- Mortality
- Quality of Life
- Left ventricular hypertrophy and left ventricular function
6.3.3 Clinical Evidence Statements

**Darbepoetin vs. Epoetin α**

*Haemodialysis Patients*

**Efficacy**

6.3.3.1 A mean change in Hb level between baseline and evaluation periods of 0.13 g/dL (95% CI –0.08 to 0.33) was above the pre-defined margin of -1.0 g/dL and therefore implied no significant difference was observed between the two treatment groups.°

Level 1+

6.3.3.2 No significant difference was observed for haemoglobin variability assessed as variance in haemoglobin; % values within the Hb target range; % values within the therapeutic range and instability of Hb levels requiring a dose change within the two treatment groups.

Level 1+

6.3.3.3 Dose change from baseline to evaluation was similar for both treatment groups.

Level 1+

6.3.3.4 The number of patients with dose changes during the titration and evaluation periods was similar for both treatment groups.

Level 1+

**Safety**

6.3.3.5 The type and frequency of adverse events was similar in both treatment groups, with no antibody formation to either treatment detected.

Level 2+

**Darbepoetin vs. Epoetin β**

*Haemodialysis patients*

**Efficacy**

6.3.3.6 There was no significant difference in maintaining Hb at 11-12 g/dl between darbepoetin (N=81) and epoetin beta (N=81), both administered s.c. weekly over 9 months.

Level 1+
**Dose**

6.3.3.7 Over the 9 months study duration, median dose fell in the darbepoetin arm (P=0.006), but increased in the epoetin beta arm (P=0.002). When converted into the same units (IU/kg/week) using the manufacturer’s dose conversion, darbepoetin dose required to achieve the same Hb outcome was significantly lower than epoetin beta dose at 9 months by 95% CI 17 to 61 IU/kg/week (P<0.001).\(^{189}\)

**Level 1+**

**Blood pressure**

6.3.3.8 BP did not change significantly in the course of the study in either treatment arm.\(^ {189}\)

**Level 1+**

**6.3.4 Health Economics Methodological Introduction**

6.3.4.1 Only one economic evaluation\(^ {190}\) was found to assess an epoetin alpha and darbepoetin comparison. However, this study did not meet quality criteria and therefore no evidence statements were made.

**6.3.5 From Evidence to Recommendations**

6.3.5.1 The GDG agreed that the evidence statements from study\(^ {187}\) on efficacy support the summary that there is no difference between EPO\(_\alpha\) and Darbepoetin for the outcomes measured, in a selected group of patients who were stable.\(^ {187}\)

6.3.5.2 Evidence statements from study\(^ {189}\) on efficacy suggest that both EPO\(_\beta\) and Darbepoetin effectively maintain target haemoglobin levels. In unselected patients on haemodialysis reduction of the dose frequency of EPO\(_\beta\) from thrice weekly to weekly may reduce efficiency and necessitate an increased dose. Based on current tendering prices, the GDG concluded that a first choice of ESA could be given in a recommendation. This allows flexibility to take local supply contracts into account.

**6.3.6 Recommendations**

6.3.6.1 The choice of ESA should be discussed with the patient 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. (A)
6.4 Early or Deferred ESA Treatment

6.4.1 Clinical Introduction

6.4.1.1 The patients most likely to derive the greatest long-term benefit from correction of anaemia are those with chronic kidney disease who are pre-dialysis. Early intervention to correct anaemia has the potential to impact on the progression of chronic kidney disease and affect patient morbidity, hospitalisation rates, quality of life, and mortality. The key goals in the management of anaemia are increased exercise capacity, improved quality of life, improved cognitive function, improved sexual function, reduced transfusion requirements, regression/prevention of left ventricular hypertrophy, improved morbidity, prevention of progression of renal disease, reduced risk of hospitalisation, and reduced mortality.

6.4.2 Methodological Introduction

6.4.2.1 A comprehensive literature search identified two studies \textsuperscript{191,192}.

6.4.2.2 Of note:

- One study \textsuperscript{191} was conducted in a selected patient population, recruiting only patients without diabetes
- Target Hb levels in both studies were not met. The target Hb level for one study \textsuperscript{191} was 13 g/dl, however Hb levels achieved were 12.9 ± 0.4 (SD) g/dl in the early treatment group and 10.3 ± 1.0 (SD) g/dl in the deferred treatment group
- The target Hb levels for one study \textsuperscript{192} were 12-13 g/dl in the early treatment group and 9-10 g/dl in the deferred treatment group, whilst levels achieved were 12.1 ± 1.4 (SD) g/dl and 10.8 ± 1.3 (SD) g/dl, respectively

6.4.2.3 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

6.4.3 Evidence Statements

\textit{Left ventricular mass index}

\textit{Pre-dialysis patients}

6.4.3.1 In a 2-year study conducted to maintain Hb 12-13 g/dl (N=75) vs. 9-10 g/dl (N=80), using epoetin and initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time, no significant differences were observed in left ventricular mass index measurements \textsuperscript{192}.

\textbf{Level 1++}
6.4.3.2 In a 2-year study conducted to maintain Hb 12-13 g/dl (N=75) vs. 9-10 g/dl (N=80), using epoetin and initiated in the latter group when Hb was <9 g/dl at two consecutive assessments 2 months apart or <8 g/dl at any one time, no significant differences between the two groups were observed in renal function as determined by glomerular filtration rate (eGFR), although GFR progressively decreased in the 2 treatment arms (P<0.001) 192.

Level 1++

6.4.3.3 In a study conducted over 22.5 months in patients without diabetes with similar baseline creatinine clearance levels, where initiation of epoetin treatment was early (N=45) vs. deferred (N=43, Hb <9 g/dl) and administered to achieve a target Hb ≥13 g/dl, the adjusted relative hazard for doubling of serum creatinine, renal replacement or death was 0.37 (95% CI 0.18 to 0.73, P=0.004) in the early epoetin treatment arm. Additionally, the risk of an event increased 2.23-fold (95% CI 1.56 to 3.18, P<0.01) per 1 mg/dl higher serum creatinine at baseline. Similarly, the adjusted relative hazard for renal replacement or death was 0.38 (95% CI 0.19 to 0.76, P=0.006) in the early epoetin treatment arm and the risk of an event increased 2.25-fold (95% CI 1.57 to 3.23, P<0.001) per 1 mg/dl higher serum creatinine at baseline 191.

Level 1+

Hypertension

6.4.3.4 In a study conducted over 22.5 months in non-diabetic patients with similar baseline creatinine clearance levels, whereby initiation of epoetin treatment was early (N=45) vs. deferred (N=43, Hb <9 g/dl) and administered to achieve a target Hb ≥13 g/dl, no significant differences were observed in systolic and diastolic blood pressure 192.

Level 1++

Quality of life

6.4.3.5 In a 2-year study conducted to maintain Hb 12-13 g/dl (N=75) vs. 9-10 g/dl (N=80), using epoetin and initiated in the latter group when Hb was <9 g/dl at 2 consecutive assessments 2 months apart or <8 g/dl at any one time, no significant
differences were observed in quality of life domains, as assessed by the Renal Quality of Life Profile and Short Form 36 (SF-36) questionnaires\textsuperscript{192}.

**Level 1++**

6.4.4 From Evidence to Recommendations

6.4.4.1 Both studies presented in the evidence were considered to be methodologically sound. The group discussed that the study by Gouva et al.,\textsuperscript{191} had achieved the study aims (in terms of level of Hb achieved) and showed a significant reduction in rate of renal progression. The study by Rogers et al.,\textsuperscript{192} did not achieve the study aim and showed no significant difference in any outcome. It was not considered possible to reach any sound conclusions on the basis of these papers.

6.4.4.2 The GDG felt they would be unable to make any recommendations on this area based on these studies alone.

6.5 Co-ordinating Care

6.5.1 Clinical Introduction

6.5.1.1 During the last decade the management of anaemia associated with chronic kidney disease in the UK has evolved into a nurse led programme in many renal units. The introduction of specialist nurses dedicated to managing anaemia in CKD has developed in response to the increase in the number of patients receiving treatment of their renal anaemia. The inefficient use of ESA’s, the increase in the use of intravenous iron therapy, the requirement for patient monitoring and for regular audit have also highlighted the need to have a dedicated person responsible for anaemia management. Specialist nurses are able to work within protocols, become supplementary and extended nurse prescribers, and therefore can manage this group of patients with a high degree of independence. This role may also be undertaken by other health professionals, such as pharmacists, the goal being to deliver an effective, efficient, patient-centred anaemia service.

The exact role of these health professionals will depend on how the anaemia management programme is set up and run, and this will vary from unit to unit.

6.5.1.2 Example: They may be responsible for a small case load such as haemodialysis patients & the management may be lead by a computer algorithm or clinicians; or they may be responsible for managing the entire anaemia programme across all modalities.
6.5.2 Methodological Introduction

6.5.2.1 A comprehensive literature search identified a before and after study \(^{193}\), however, due to methodological limitations it was excluded from the evidence statements.

6.5.2.2 A comprehensive literature search did not identify any health economic studies that were suitable to address this issue.

6.5.3 From Evidence to Recommendations

6.5.3.1 The GDG felt that there is a benefit to having a health care worker identified as having responsibility for the provision of care of specific patients. There are core social and professional skills that will be needed which can be delivered by people from different clinical backgrounds e.g. nurses or pharmacists. The cost-effectiveness varies according to the activity of the anaemia co-ordinator and improves with increasingly independent activity.

6.5.4 Recommendations

6.5.4.1 Patients should have access to a designated contact person or persons who have principal responsibility for their anaemia management and who have skills for the following activities: (D (GPP))

- Monitoring and managing a caseload of patients in line with locally agreed protocols
- Providing information, education and support to empower patients 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 seamless service of the highest standard
- Prescribing medicines related to anaemia management and monitoring their effectiveness

6.6 Providing ESAs

6.6.1 Clinical Introduction

6.6.1.1 Patients with anaemia associated with CKD do not necessarily need to receive their treatment within a hospital setting. One of the core principles involved in improving health outcomes for people with long term conditions is improved care in
primary care and community settings, emphasising the patient’s role in self care and thus promoting independence and empowering patients to allow them to take control of their lives. Provision of ESA treatment is no different and can only be achieved with an appropriate infrastructure and an effective delivery system enabling the right patients to get the right ESA at the right time and in the right place.

6.6.2 Methodological Introduction

6.6.2.1 A comprehensive literature search identified one cross-sectional study\textsuperscript{162}.

6.6.2.2 A comprehensive literature search did not identify any health economic studies that were suitable to address this issue.

6.6.3 Evidence Statements

_pre-dialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients_

6.6.3.1 In a cross-sectional study\textsuperscript{162}, of N=87 patients, ESA supply was found to be mostly by GPs (71%), followed by hospital pharmacy (29%), although 20 patients (23%) reported that their GPs had refused to supply ESA. Of N=124 patients, 51% reported to prefer obtaining their ESA supplies from community pharmacy, whilst 19% preferred hospital pharmacy. The combined reasons for both community and hospital pharmacy were primarily convenience (55%), followed by easier access (16%), supply always available (13%), shorter waiting time (10%) and larger supply provided (6%).

6.6.4 From Evidence to Recommendations

6.6.4.1 One cross-sectional study showed that there were issues for patients in obtaining ESA supplies from GPs and that many patients obtained their drugs from community pharmacists or the hospital pharmacy. This study was completed prior to the introduction of home delivery schemes run by pharmaceutical companies. However, there was often little flexibility in the day / time that companies could provide a home delivery service to patients. Hospitals source the cheapest supply of ESAs from the drug companies and cost was also an important factor in the provision of ESAs. However, every patient should have a secure supply of ESAs that were obtained from a source that took the patients choice and lifestyle into consideration.
6.6.4.2 It was noted that maintaining choice for patients in how ESAs are supplied and administered was vital as some patients were dependant on hospitals to administer drugs or did not have the facilities to store large quantities of drugs.

6.6.5 Recommendations

6.6.5.1 In order that treatment is clinically effective, consistent, safe and patient centred, the prescriber should agree a plan with the patient, which is revised as the patient’s needs or circumstances change and which takes into account: (D (GPP))

- Providing a secure drug supply to the patient
- Flexibility of where the drug is delivered and administered
- The lifestyle and preferences of the patient
- Cost of drug supply
- A desire for self-care where appropriate

6.7 ESAs: Optimal Route of Administration

6.7.1 Clinical Introduction

6.7.1.1 Three ESAs are currently available in the UK, 2 short-acting (EPOα and EPOβ) and 1 long-acting (Darbepoetin). Short-acting ESAs are suitable for short dose intervals and long-acting ESAs are more suited to dosing intervals of at least a week or more. EPOβ and Darbepoetin are licensed for both subcutaneous and intravenous administration, EPOα is only currently licensed for intravenous administration. Intravenous administration of ESAs obviously requires intravenous access and is therefore logistically difficult in pre-dialysis, peritoneal dialysis, and transplant patients. Patients on haemodialysis treatment may therefore easily receive ESA treatment by any route, and at varying dose intervals, whereas other patients with anaemia associated with CKD will normally require subcutaneous administration with dosing intervals largely determined by the ESA used.

6.7.2 Methodological Introduction

6.7.2.1 A literature search identified fifty-eight studies. Due to the high number of retrieved studies, studies were grouped into the various identified factors and only the studies describing clinically relevant factors of the highest level of evidence and
those which used regression analysis were included in the evidence statements. These are detailed below:

Table 29:

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>194</td>
<td>RCT</td>
</tr>
<tr>
<td>195</td>
<td>RCT, cross-over</td>
</tr>
<tr>
<td>196</td>
<td>RCT</td>
</tr>
<tr>
<td>197</td>
<td>RCT</td>
</tr>
<tr>
<td>198</td>
<td>RCT, cross-over</td>
</tr>
<tr>
<td>199</td>
<td>RCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>RCT</td>
</tr>
<tr>
<td>201</td>
<td>RCT</td>
</tr>
<tr>
<td>202</td>
<td>RCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
<td>Non-randomised study</td>
</tr>
<tr>
<td>204</td>
<td>Cohort study</td>
</tr>
<tr>
<td>205</td>
<td>Cohort study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>206</td>
<td>Prospective longitudinal study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient preference</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>207</td>
<td>Prospective cross-sectional cross-over study</td>
</tr>
</tbody>
</table>

6.7.2.2 Four studies\(^{208,209,210,211}\) were excluded from the evidence statements due to methodological limitations.

6.7.2.3 The GDG agreed the following outcomes were priorities:

- Mortality
- Morbidity
- Quality of life
- Pain
- Hb/Hct levels
- Complications
- Patient satisfaction
- Patient concordance
• Patient compliance
• ESA dose required

6.7.2.4 A comprehensive literature search found no suitable health economic studies to address this issue.

6.7.3 Evidence Statements

**Blood pressure**

*Haemodialysis patients*

6.7.3.1 A 6-month study\(^{206}\) conducted in hypertensive patients (N=13) found no significant changes in Hct after conversion of epoetin administration from the i.v. route to the s.c. route. However, a significant decrease of predialysis mean arterial pressure from the first month was observed (P<0.05).

**Level 3**

*Continuous Ambulatory Peritoneal Dialysis (CAPD) patients*

6.7.3.2 In a 16-week RCT\(^ {197}\), a mean epoetin dose of 84 ± 9 U/kg/week administered s.c. vs. a mean dose of 133 ± 7 U/kg/week administered i.p. increased antihypertensive therapy in both groups, but no significant difference was found between the two groups.

**Level 1+**

*Patient preference*  

*Haemodialysis patients*

6.7.3.3 A study investigating pain of two brands of epoetin administered by the s.c. route (N=32) found pain assessed by the Visual Analogue Scale was higher in patients when epoetin \(\alpha\) was administered when compared to epoetin \(\beta\) or 0.9% saline (P<0.0001)\(^ {207}\).

**Level 3**

In an RCT study (N=208) comparing three times weekly i.v. vs. three times weekly s.c.\(^ {196}\), level of discomfort assessed using the Visual Analogue Scale found similar scores between the two modes of administration.

**Level 1++**

*Patient population*
**Haemodialysis vs. Continuous Ambulatory Peritoneal Dialysis (CAPD) patients**

6.7.3.4 In a 130-day non-randomised study investigating epoetin administration by the s.c. vs. the i.v. route (N=29), the time and cumulative dose required to achieve a target Hb of 11.3 g/dl was lower in the s.c. treated HD (N=9) and CAPD groups (N=9) (both P<0.05) when compared to the i.v. treated HD group (N=11). In addition, once target Hb was achieved, a lower epoetin dose was required in the HD and CAPD s.c. groups (P<0.05) when compared to the i.v. treated HD group. There were no differences in epoetin dose requirement between the s.c. treated HD and CAPD groups.

In agreement with this finding, no differences were observed in both Hb/Hct levels and epoetin requirement over 6 months in a cohort study comparing epoetin administration by the s.c. route in CAPD (N=8) vs. HD (N=7) patients.  
**Level 2**

6.7.3.5 In contrast to the above findings, a 24-week cohort study comparing HD (N=10) vs. CAPD (n=11) when epoetin was administered by the s.c. route found epoetin requirement to achieve and maintain target Hct of 30% was higher in the HD group (both P<0.05).

**Level 2**

**Frequency of administration**

**Haemodialysis patients**

6.7.3.6 Three RCTs of 12-16 weeks duration investigating s.c. epoetin administration once weekly vs. twice weekly and once weekly vs. three times weekly found no significant difference in epoetin requirement and rise in Hb levels or systolic BP in both groups.

**Level 1**

**Efficacy**

**Haemodialysis patients**

6.7.3.7 Four RCTs of 12 month duration, 8 to 24-week active treatment duration with 24-week follow-up period, 48-week duration consisting of a 26-week maintenance phase and 4-month duration, investigating s.c. vs. i.v. epoetin administration three times weekly found no significant differences in Hb/Hct levels between the two groups, although time to reach the target Hb was higher in the i.v. treated group (P=0.037) of one study.

6.7.3.8 One study found no significant differences between the two modes of administration of epoetin in the weight-standardised epoetin doses at monthly intervals and cumulative epoetin dose to target Hct 28-36%. One other study initially found greater epoetin requirement in the i.v. group (P=0.019) during the Hb stabilisation phase of the study, but once target Hb was achieved in both groups,
no difference was observed between the two groups, whilst two other studies \(^{199}\), 32\% \(^{196}\) found epoetin requirement was less via the s.c. route (P=0.02).

6.7.3.9 In addition, quality of life assessed using the Kidney Disease Questionnaire in one study \(^{157}\) showed improvement in the physical and fatigue domains of both the i.v. and s.c. groups. These improvements, however, did not differ between the two routes of administration at any time.

**Level 1+ and 1++**

6.7.3.10 Converse to the above findings, in a randomised cross-over study patients received similar doses of epoetin s.c. once (A1), twice- (A2) or thrice-(A3) weekly (N=43), and compared to patients receiving epoetin i.v. once (B1), twice (B2) or three times (B3) weekly (N=38) over 3 months and then by the alternative route for another 3 months \(^{198}\). When both groups were combined, the Hb changes for all patients when treated with s.c. epoetin for 3 months, a rise (P<0.001) in Hb was noted, whereas, i.v. epoetin for 3 months produced a fall in Hb (P<0.001).

**Continuous Ambulatory Peritoneal Dialysis (CAPD) patients**

6.7.3.11 In a 16-week RCT (N=19), s.c. administered epoetin produced a rise in Hb levels (P<0.01), whereas i.p. administered epoetin did not, despite a higher mean \(^{197}\).

**Peritoneal Dialysis patients**

6.7.3.12 Similarly to the CAPD patients, in a 32-week randomised cross-over study (N=13) \(^{195}\), Hb levels in patients with epoetin administered i.p. fell (P=0.03) when compared to patients who received it by the s.c. route. In support of this finding, the 16-week area under the Hct response curve (P=0.0010) and the mean slope of the 16-week Hct response curve (P=0.05) was greater for s.c. when compared to i.p. dosing. Consequently, epoetin requirement per week was greater in the i.p. group with the 16-week dose requirement area under the curve (P=0.0029) and the slope of the 16-week dose requirement curve (P=0.017) being greater for the i.p. route. In addition, the mean total dose per week over the entire study was greater via the i.p. route (p<0.01).

**Level 1+**

6.7.4 From Evidence to Recommendations

6.7.4.1 Of the factors addressed, hypertension was not shown to be affected by the route of administration of ESAs. The patient population, pain of injection, frequency of
administration, efficacy and cost, were all important factors in determining the route of administration.

6.7.4.2 The following points were also relevant:

- It was not practicable to administer ESAs by the intravenous route in patients not on haemodialysis. Equally, patients on haemodialysis may prefer to receive their ESA via the i.v. route.
- Frequency of administration was also considered important for nursing compliance. In some units it was considered better to give ESAs routinely at all dialysis visits rather than at every third.
- The half-life of the drug also determines the frequency of administration.
- With regards to efficacy, administration via the s.c. route using short-acting ESAs required up to 30% less drug to be administered.

6.7.5 Recommendations

6.7.5.1 The patient 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: (C)

- Patient population (e.g. haemodialysis patients)
- Pain of injection,
- Frequency of administration,
- The lifestyle and preferences of the patient
- Efficacy (e.g. subcutaneous versus intravenous, or long-acting versus short-acting preparations)
- Cost of drug supply

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. (A)
6.8 ESAs: Dose and Frequency

6.8.1 Clinical Introduction

6.8.1.1 Currently ESAs available fall into 2 broad classes, short- and long-acting. The characteristics of long-acting ESAs are such that when using these agents the shortest dose interval is weekly, with no appreciable difference between subcutaneous and intravenous routes of administration. With short acting ESAs dose intervals of a week or more are less cost-effective than shorter dose intervals, and the subcutaneous route of administration is more cost effective than the intravenous route when using these agents.

6.8.1.2 In patients without renal disease studies looking at erythropoietin response to anaemia show an exponential rise in serum EPO levels with falling haemoglobin, suggesting that with increasing severity of anaemia the natural 'endogenous' EPO dose is initially high and subsequently tails off as the anaemia corrects. Although it would be logical to attempt to mimic this, in practice too rapid correction of anaemia in the early days of ESA treatment was associated with significant adverse effects (reference to be added). The dose and frequency of administration of ESA is therefore likely to depend on haemoglobin level and rate of change of haemoglobin, the class of ESA used and (in the case of short-acting ESAs) the route of administration, the CKD population under treatment, and various patient factors and patient preferences.

6.8.2 Methodological Introduction

6.8.2.1 A literature search identified nine studies. Two studies had methodological limitations and were therefore excluded from the evidence statements. As the meta-analysis addressing route of administration had methodological limitations, the ten studies within it were individually appraised and five met quality criteria.

6.8.2.2 The clinically relevant factors and respective study types are detailed below:

Table 30: Summary of included studies

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies included in the meta-analysis</td>
<td>RCT</td>
</tr>
</tbody>
</table>

Anaemia in CKD: full guideline DRAFT (January 2006)
6.8.2.4 The GDG agreed that the outcomes of priority were Hb levels, rate of Hb correction and complications.

6.8.2.5 Of note:
- Due to methodological limitations, one RCT study\textsuperscript{215} was downgraded to Level 2 in the evidence hierarchy
- Adjuvant RBC transfusions were administered in addition to epoetin during the study period in four studies\textsuperscript{213, 219,220,196}
- Two studies addressing rate of Hb correction\textsuperscript{219, 217} were conducted in children

6.8.3 Evidence Statements

Route of administration

\textit{Haemodialysis patients}

Table 31:
<table>
<thead>
<tr>
<th>Study reference</th>
<th>Evidence hierarchy</th>
<th>ESA treatment arms</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 212             | Level 2++          | Once weekly s.c. vs. Once weekly i.v. | - The number of patients who maintained a stable Hb level (defined as a decrease of ≤1 g/dl) was similar in both groups  
- Decrease (P<0.05) in Hb concentration in the i.v. treated group when the evaluation phase of the study was compared to the dosing phase  
- Increased (P<0.05) mean weekly dose of epoetin alfa needed to maintain individual target Hb levels in the i.v. group |
| 196             | Level 1++          | three times weekly i.v. vs. three times weekly sc. | - Hb and Hct were similar in both groups  
- average weekly epoetin dose was lower (P=0.002) in the s.c. group |
| 199             | Level 1++          | s.c. vs. i.v. | - Mean Hb levels were stable and remained equivalent in both groups at the end of the study  
- Epoetin requirement was found to be less (P=0.02) when administered by the s.c. route. When the different dosing strata were studied (i.e. >150 U/kg/week vs. 100-150 U/kg/week vs. <100 U/kg/week), it was evident that this difference was only in patients with the highest epoetin needs (>150 U/kg/wk) |
| 223             | Level 2+           | s.c. vs. i.v. | - Hct levels were similar over the entire study period |
| 194             | Level 1+           | three times weekly s.c. vs. three times weekly | - Weight-standardised epoetin doses at monthly intervals and cumulative |
i.v.

---

157 Level 1+ three times weekly s.c. vs. three times weekly i.v.

- Although time to reach the target Hb was longer (P=0.037) in the i.v. treated group, mean Hb and Hct levels were similar in both groups
- Epoetin requirement was greater (P=0.019) in the i.v. group during the Hb stabilisation phase of the study, but once target Hb was achieved in both groups, no difference was observed between the two groups.

6.8.3.1 A meta-analysis of the four level 1 studies addressing epoetin dose when administered SC vs. IV found a lower epoetin requirement when administered SC (WMD –30.05 (95% CI –43.96 to –16.14) $I^2 = 7\%$). This was in support of the findings of the excluded heterogeneous meta-analysis. A sensitivity analysis excluding the study with sample size N<20 was also in agreement with this finding and ruled out heterogeneity (WMD –41.61 (95% CI - 60.66 to –22.55) $I^2 = 0\%$).

### Starting Hb level

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Patient population</th>
<th>Evidence hierarchy</th>
<th>Hb level at baseline</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>Continuous Ambulatory Peritoneal Dialysis (CAPD)</td>
<td>Level 3</td>
<td>≤7.5 g/dl vs. &gt;7.5 g/dl</td>
<td>• Time to achieve Hb target was longer (P&lt;0.001) in the lower Hb group at 6 months despite similar rate of Hb increase and epoetin dose in both groups</td>
</tr>
<tr>
<td>219</td>
<td>Children on haemodialysis</td>
<td>Level 3</td>
<td>&lt;6.8 g/dl vs. ≥6.8 g/dl</td>
<td>• A similar proportion of each group (81% vs. 80%) reached the</td>
</tr>
</tbody>
</table>
target Hb of 9.6-11.2 g/dl
• The median time to achieve target Hb was higher in the lower Hb group (median 13 weeks vs. 9 weeks; P value not reported by the authors)

**Hypertension**

**Haemodialysis patients**

Table 33:

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Evidence hierarchy</th>
<th>ESA treatment arms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>214</td>
<td>Level 3</td>
<td>i.v. three times weekly</td>
<td>• No change in mean systolic and diastolic blood pressures was found, and only 3 of 24 patients who had required treatment for hypertension before epoetin therapy required an increased dose of antihypertensive medication</td>
</tr>
<tr>
<td>215</td>
<td>Level 2+</td>
<td>Hct 40.8 ± 5.2% vs. Hct 30 ± 4.3%</td>
<td>• No differences were found in mean daytime systolic or diastolic BP and mean night time systolic or diastolic BP between the two groups</td>
</tr>
</tbody>
</table>
### 4) Rate of Hb correction

**Table 34:**

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Patient population</th>
<th>Evidence hierarchy</th>
<th>ESA treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>216</td>
<td>Pre-dialysis</td>
<td>Level 3</td>
<td>s.c. twice weekly</td>
<td>• There was a rise in Hb and Hct when compared to baseline levels after 3 months, which was sustained after 6 months and 12 months (all P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Target Hb was achieved 10-11 g% after 6 months</td>
</tr>
<tr>
<td>219</td>
<td>Children on haemodialysis</td>
<td>Level 3</td>
<td>i.v two to three times weekly</td>
<td>• A median time to target of 11 weeks was achieved with a median dose of 150 U/kg/week in 81% of patients. The mean rate of Hb rise was 0.5 g/dl per 4 weeks in patients receiving the starting dose of 75 U/kg/week and 0.8 g/dl per 4 weeks in those whose dose had been increased to 150 U/kg/week (P value not reported by the authors)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>218</td>
<td>Haemodialysis</td>
<td>Level 2+</td>
<td>same weekly epoetin alfa dose in varying dose intervals</td>
<td>• Patients who received 4,000 U epoetin as a bolus injection did not require increased epoetin doses, but dosing intervals significantly increased (P=0.01), unlike patients who received 10,000 U epoetin at intervals who required higher epoetin doses (P=0.002) with reduced dosing intervals (P=0.0001) to maintain Hb &gt;11</td>
</tr>
<tr>
<td>220</td>
<td>Peritoneal dialysis patients</td>
<td>Level 1+</td>
<td>5, 10 and 20 U/kg epoetin daily s.c., to target Hct 30-35%,</td>
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<td>----------------------------------------------------------</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• The differences in the mean weekly change in Hct were significant (P&lt;0.05) over the 8 week constant-dose phase, between all three groups, in ascending order</td>
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<td></td>
<td></td>
<td></td>
<td>• During the correction phase, the time to achieve the target Hct in 50% of the patients (total N=72) who received 5, 10 and 20 U/kg daily s.c. was 154, 119 and 92 days respectively and the median cumulative epoetin doses to reach target Hct were calculated as 1494, 1523 and 1678 U/kg respectively</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>217</th>
<th>Post-transplant paediatric patients with chronic allograft dysfunction</th>
<th>Level 3</th>
<th>Thrice weekly s.c. vs. twice weekly s.c. vs. once weekly s.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• There was an increased Hct in 84% of the children from 23.2% ± 3.1% to 33% ± 3.1% (P value not reported by the authors) within 7.2 ± 4.9 weeks at a mean rate of 1.98% per week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hct increase and epoetin starting dose were linearly related (r=0.44, P&lt;0.05)</td>
</tr>
</tbody>
</table>
6.8.4 Health Economics Methodological Introduction

6.8.4.1 One study\textsuperscript{224} was identified in a literature search. Three studies\textsuperscript{222,173,225} did not meet quality criteria. The included study\textsuperscript{224} estimated the increased costs of changing from SC epoetin to IV epoetin in a retrospective analysis of 99 haemodialysis patients over 7-months.

6.8.4.2 A cost-minimisation analysis was conducted at the request of the GDG to compare subcutaneous and intravenous epoetin administration. Full details are given in Appendix D.

6.8.5 Evidence Statements

6.8.5.1 The mean dose in the ‘SC switched to IV’ patients increased significantly (+46.83 + 10.20 UI/kg/week, +34.9%, p=0.001) over 7 months and was estimated to increase costs by $1,841 \pm 401$ Euro (2002) per patient per year (+26.3%)\textsuperscript{224}.

6.8.5.2 The cost-minimisation analysis presented to the GDG stated in conclusion: “The subcutaneous route of administration of epoetin vs. intravenous route results in cost savings of approximately £1,100 + £727 per patient per year.”

6.8.6 From Evidence to Recommendations

6.8.6.1 Of the factors addressed, hypertension was not shown to have an effect in determining the dose and frequency of ESAs required to correct anaemia. But the route of administration and the rate of correction were important factors.

6.8.6.2 An acceptable rate of rise of haemoglobin was considered to be \textasciitilde1-2g/dL/month. In general, it was thought that a patient’s pre-treatment starting level of Hb would not influence the starting dose of ESA, but that their subsequent haemoglobin response would influence the dose thereafter.

6.8.6.3 Hypertension should be treated prior to the administration of ESAs. It was stated that episodes of severe hypertension would temporarily alter the dose of ESA, but that generally hypertension would not affect this issue.
6.8.6.4 The included health economic study supported the excluded meta-analysis\textsuperscript{222} that intravenous administration of short-acting ESAs was more costly than subcutaneous administration.

6.8.6.5 The group concluded that in general s.c. administration leads to a reduced dose of short acting EPO. One study indicated that this was only relevant during the stabilisation phase but not during the maintenance phase of treatment.

6.8.7 Recommendations

6.8.7.1 When correcting anaemia of CKD, the dose and frequency of ESAs should be:
- determined by the duration of action and route of administration of the ESA (B)
- adjusted to keep the rate of Hb increase between 1 and 2g/dL/month (D(GPP))

6.9 Optimal Hb Levels

6.9.1 Clinical Introduction

6.9.1.1 The optimal haemoglobin range to be maintained following correction of anaemia associated with CKD is that which confers the most benefit and least adverse effect in the most cost effective way.

6.9.1.2 The key questions are: do patients with higher haemoglobin levels do well because they are less sick, and is it because they are less sick that they attain higher haemoglobin levels? Or is there a causal relationship between higher haemoglobin levels and lower risks of morbidity and mortality, and if so what is the optimal haemoglobin range to be maintained?

6.9.2 Clinical Methodological Introduction

6.9.2.1 A literature search identified one meta-analysis\textsuperscript{226} containing nineteen RCTs, which assessed the effects of lower vs. higher haemoglobin collectively in predialysis, peritoneal dialysis and haemodialysis patients attained by means of ESA therapy or blood transfusion. The findings were stratified into two categories, namely studies that compared treatment to two haemoglobin ranges, higher (11.9-
15.0 g/dL) vs. lower (9.0-12.0 g/dL) (7 studies) and those which assessed the effects of epoetin (Hb 9.5-13.3 g/dL) vs. no treatment (Hb 7.5-10.4 g/dL) (12 studies).

6.9.2.2 An additional three RCTs \(^{227,228,229}\) and a prospective longitudinal study \(^{230}\) were found which addressed the effects of lower vs. higher Hb levels.

6.9.2.3 The different Hb levels examined and study durations need to be accounted for when evaluating the evidence is summarised in the table below:

Table 35:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study duration</th>
<th>Low Hb (g/dL)</th>
<th>High Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>226</td>
<td>6 to 29 months</td>
<td>9.0-12.0</td>
<td>11.9-15.0</td>
</tr>
<tr>
<td>226</td>
<td>2 to 12 months</td>
<td>7.5-10.4</td>
<td>9.5-13.3</td>
</tr>
<tr>
<td>228</td>
<td>8 months</td>
<td>9.0</td>
<td>12.0</td>
</tr>
<tr>
<td>231</td>
<td>24 months</td>
<td>10.9 ± 0.7</td>
<td>12.6 ± 1.0</td>
</tr>
<tr>
<td>230</td>
<td>8 months</td>
<td>10.5 ± 0.9</td>
<td>13.4 ± 3.1</td>
</tr>
</tbody>
</table>

6.9.2.4 Of note:

- Although the meta-analysis \(^{226}\) was of rigorous methodology leading to a systematic review of a high standard, the trials within it were of variable quality
- The meta-analysis \(^{226}\) was heavily weighted by a single study \(^{232}\) conducted in haemodialysis patients with severe cardiovascular disease, which may imply unsuitability for extrapolation to the entire CKD patient population
- Although two studies in the meta-analysis \(^{226}\) enrolled children, the findings were not stratified on the basis of age
- Due to methodology limitations of one RCT \(^{228}\) was downgraded to Level 2+ of the evidence hierarchy
- The means of achieving target Hb in the studies included the use of ESAs and/or blood transfusions

6.9.3 Clinical Evidence Statements

Table 36: Summary of Appraised Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Outcome</th>
<th>Patient population (N)</th>
<th>Aiming for a High Hb</th>
<th>Aiming for a Low Hb</th>
<th>Evidence grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>226</td>
<td>All-cause mortality</td>
<td>Pre-dialysis, peritoneal dialysis and</td>
<td>11.9-15.0 g/dL</td>
<td>9.0-12.0 g/dL ↓</td>
<td>Level 1++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>All-cause mortality</td>
<td>Pre-dialysis, peritoneal dialysis and haemodialysis (N=1949)</td>
<td>9.5-13.3 g/dL</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>Hypertension</td>
<td>Pre-dialysis, peritoneal dialysis and haemodialysis (N=255)</td>
<td>11.9-15.0 g/dL</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>Hypertension</td>
<td>Haemodialysis (N=12)</td>
<td>12.0 g/dL ↑</td>
<td>9.0 g/dL</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>Quality of life</td>
<td>Pre-dialysis, peritoneal dialysis and haemodialysis (N=1277)</td>
<td>11.9-15.0 g/dL</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>Quality of life</td>
<td>Pre-dialysis, peritoneal dialysis and haemodialysis (N=unknown)</td>
<td>9.5-13.3 g/dL 7.5-10.4 g/dL</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>Quality of life</td>
<td>Haemodialysis (N=12)</td>
<td>12.0 g/dL</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>Physical performance-exercise radionuclide ventriculogram</td>
<td>Haemodialysis (N=12)</td>
<td>12.0 g/dL ↑</td>
<td>9.0 g/dL</td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>Physical performance-maximal incremental exercise testing</td>
<td>Haemodialysis (N=12)</td>
<td>12.0 g/dL</td>
<td>9.0 g/dL</td>
<td></td>
</tr>
<tr>
<td>233</td>
<td>6-min walking distance</td>
<td>Haemodialysis (N=596)</td>
<td>12.6 ± 1.0 g/dl</td>
<td>10.9 ± 0.7 g/dl</td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>Left ventricular mass and mass index</td>
<td>Haemodialysis (N=12)</td>
<td>12.0 g/dL</td>
<td>No difference (N.B. short study duration)</td>
<td></td>
</tr>
<tr>
<td>234</td>
<td>Left ventricular volume index</td>
<td>Haemodialysis (N=596)</td>
<td>12.6 ± 1.0 g/dl</td>
<td>10.9 ± 0.7</td>
<td></td>
</tr>
</tbody>
</table>
6.9.4 Health Economics Methodological Introduction

6.9.4.1 A cost-utility analysis study was appraised, which estimated the incremental cost per QALY of treating haemodialysis patients with epoetin doses adjusted to attain haemoglobin target ranges of 9.5 to 10.5 g/dL, 11.0 to 12.0 g/dL, 12.0 to 12.5 g/dL and 14.0 g/dL.

6.9.4.2 An economic model was constructed to evaluate the cost-effectiveness of various haemoglobin ranges in haemodialysis patients. Full details are given in Appendix C.

6.9.5 Health Economics Evidence Statements

6.9.5.1 An additional $55,295 per additional QALY gained was required to achieve the target haemoglobin range of 11.0-12.0 g/dL versus a 9.5-10.5 g/dL haemoglobin target range.

6.9.5.2 An additional $613,015 per additional QALY gained was required to achieve the target haemoglobin range of 12.0-12.5 g/dL versus a 11.0-12.0 g/dL haemoglobin target range.
6.9.5.3 An additional $828,215 per additional QALY gained was required to achieve the target haemoglobin of 14.0 g/dL versus a 12.0-12.5 g/dL haemoglobin target range.

6.9.5.4 The dose of epoetin and the estimate of health-related quality of life had the largest effect on results in the sensitivity analysis. Assuming 32% (base-case assumes 14%) lower dose requirement for subcutaneous epoetin than intravenous epoetin:

Table 37:

<table>
<thead>
<tr>
<th>Target Hb</th>
<th>Incremental cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.0-12.0 g/dL vs. 9.5-10.5 g/dL</td>
<td>$38,340</td>
</tr>
<tr>
<td>12.0-12.5 g/dL vs. 11.0-12.0 g/dL</td>
<td>$423,17</td>
</tr>
<tr>
<td>14.0 g/dL vs. 12.0-12.5 g/dL</td>
<td>$569,500</td>
</tr>
</tbody>
</table>

Base-line utility score at lower limit of 95% CI

<table>
<thead>
<tr>
<th>Target Hb</th>
<th>Incremental cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.0-12.0 g/dL vs. 9.5-10.5 g/dL</td>
<td>$59,822</td>
</tr>
<tr>
<td>12.0-12.5 g/dL vs. 11.0-12.0 g/dL</td>
<td>$663,210</td>
</tr>
<tr>
<td>14.0 g/dL vs. 12.0-12.5 g/dL</td>
<td>$896,030</td>
</tr>
</tbody>
</table>

Base-line utility score at upper limit of 95% CI

<table>
<thead>
<tr>
<th>Target Hb</th>
<th>Incremental cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.0-12.0 g/dL vs. 9.5-10.5 g/dL</td>
<td>$51,404</td>
</tr>
<tr>
<td>12.0-12.5 g/dL vs. 11.0-12.0 g/dL</td>
<td>$569,884</td>
</tr>
<tr>
<td>14.0 g/dL vs. 12.0-12.5 g/dL</td>
<td>$769,942</td>
</tr>
</tbody>
</table>

6.9.5.5 The economic model presented to the GDG stated in conclusion: “The results suggest treating anaemia with a target Hb 11-12 g/dL is cost-effective in haemodialysis patients based on a £30,000 (incremental cost-effectiveness ratio) threshold. However, there is uncertainty in the results of the model from lack of certainty in the input parameters. Nevertheless, the results are relatively robust based on one-way sensitivity analyses and threshold analyses. This analysis is a simplified model of the costs and benefits of treating anaemia in the haemodialysis population and a variety of assumptions have been used in the base-line analysis.”

6.9.6 From Evidence to Recommendations

6.9.6.1 The GDG noted that the largest meta-analysis considered was heavily skewed by one study that influenced the data on mortality. This study of patients with cardiovascular disease was terminated early due to a trend towards increased mortality in the high target haemoglobin group. Thus statistical significance between the two groups could not be achieved. The GDG accepted that most of the studies it contained did not state their method of randomisation and were not adequately blinded; only two were carried out on an intention to treat basis. It was noted that a target Hb level of 14 ± 1 g/dl (converted from Hct) was associated...
with higher mortality in a study of patients with congestive heart failure and ischaemic heart disease. The GDG thought this may have related to the large doses of iron and epoetin that had to be administered in order for a sicker patient to achieve a haemoglobin in this range\textsuperscript{226}. It was considered unhelpful both clinically and economically to administer increasing doses of epoetin and iron to a patient who was not responding adequately to the treatment. The GDG agreed with the authors of the meta-analysis that it would be prudent to ensure that patients with cardiovascular impairment maintain a Hb below 12.0 g/dl.

6.9.6.2 The GDG did not feel that increasing age should be a specific factor in setting a haemoglobin target but felt that low levels of physical activity in some individuals should be considered before setting the haemoglobin range for that individual.

6.9.6.3 The GDG highlighted that two studies within\textsuperscript{226} included children but that no outcome data was specifically recorded from this population. The GDG noted that despite a lack of direct evidence relating to children, in general, they could be expected to benefit from a similar Hb level to adults.

6.9.6.4 The GDG noted that the kinetics of a patient's response to epoetin vary. This means that whatever range of haemoglobin is specified as being optimal, it is inevitable that some patients will have a haemoglobin outside this range some of the time. This is because action to maintain the haemoglobin within the specified range may only be taken when a haemoglobin measurement falls outside the range and it will take time for any action to produce an effect. The GDG therefore agreed that they would specify a target range in the knowledge that this would result in most patients maintaining a haemoglobin concentration within 0.5g/dL either side of that specified range.

6.9.6.5 The GDG felt that setting a Hb range of 11.0 - 12.0g/dl would in effect allow the majority of patients to reach a level between 10.5 –12.5 g/dL. It was noted from anecdotal evidence that maintaining a Hb of 12g/dL could make a large difference to a patients quality of life, exercise capacity and cognitive function; the increase in physical performance was further supported by the evidence\textsuperscript{227}. The GDG also considered a health economic model that suggested haemoglobin ranges above 12 g/dL were not cost-effective because of the high cost of epoetin and low incremental QALYs gained from higher haemoglobin ranges\textsuperscript{239}.

6.9.6.6 The consensus amongst the GDG that a range of 11.0 –12.0 g/dL was consistent with both the clinical and health economic evidence.
6.9.7 Recommendations

6.9.7.1 In adults with anaemia of chronic kidney disease, treatment should maintain stable haemoglobin (Hb) levels between 10.5 and 12.5 g/dL. Adjusting treatment should typically be considered when Hb rises above 12.0 or falls below 11.0 g/dL. (C) Patient preferences, symptoms and comorbidity should be taken into account and the aspirational range and action thresholds revised accordingly. (C) For children aged 2 years and over, haemoglobin range should be maintained at the target range for adults. For children aged under 2 years, treatment should maintain stable haemoglobin levels between 10 and 11 g/dL, reflecting the lower normal range in that age group. (D(GPP))

6.9.7.2 In patients who do not achieve a haemoglobin level above 10.5 g/dL despite correction of iron deficiency and exclusion of the known causes of resistance to erythropoietin therapy (treatment with \( \geq 300 \) IU/kg/week of erythropoietin or equivalent dose of darbepoetin), lower levels of haemoglobin may have to be accepted. (D(GPP))

6.9.7.3 Age alone should not be a determinant for treatment of anaemia of CKD. (D(GPP))

See 3.2.4 for the associated algorithm.

6.10 Optimum haemoglobin levels in children with anaemia of CKD

6.10.1 Methodological Introduction

6.10.1.1 The two RCTs conducted in children\(^\text{i}\), one of cross-over design\(^\text{j}\), which were reported in the meta-analysis\(^\text{k}\) used to address the effects of lower vs. higher haemoglobin were individually appraised. An additional cross-over RCT study\(^\text{l}\) that was conducted in the same paediatric population was also appraised.

6.10.1.2 Issues for consideration:

- The two cross-over RCTs\(^\text{m},^\text{n}\) were downgraded to Level 2+ due to methodological limitations
- One study\(^\text{o}\) had set out to investigate dosing requirements
• Study duration to assess cardiovascular benefits of epoetin administration \textsuperscript{242} may not have been sufficiently long at 48 weeks

Table 38: Summary characteristics of appraised studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target Hb</th>
<th>Study type</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>240</td>
<td>44</td>
<td>&gt;-2 SD below mean for age, but ≤ mean Hb for age</td>
<td>RCT of Low dose vs. high dose epoetin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>242</td>
<td>7</td>
<td>10.5 to 12.0 g/dl</td>
<td>Cross-over RCT of epoetin vs. placebo</td>
<td>24 weeks in each limb, 48 weeks total</td>
</tr>
<tr>
<td>241</td>
<td>7</td>
<td>10.5 to 12.0 g/dl</td>
<td>Cross-over RCT of epoetin vs. placebo</td>
<td>24 weeks in each limb, 48 weeks total</td>
</tr>
</tbody>
</table>

6.10.2 Evidence Statements

Table 39:

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertension and cardiovascular parameters</th>
<th>Patient population (N)</th>
<th>Achieved high Hb</th>
<th>Achieved low Hb</th>
<th>Evidence grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>240</td>
<td>Systolic and diastolic BP</td>
<td>Children on haemodialysis, peritoneal dialysis and pre-dialysis (N=44)</td>
<td>12.9 ± 0.7; 11.9 ± 1.6; 12.7 ± 2.0 g/dl</td>
<td>8.4 ± 1.0; 10 ± 2.0; 11.9 ± 1.8 g/dl</td>
<td>Level 1+</td>
</tr>
<tr>
<td>242</td>
<td>Cardiac index (P=0.01), ventricular stroke index (P=0.03), heart rate (P=0.002), aortic stroke distance (P=0.01), minute distance (P=0.03) and left ventricular end diastolic diameter (P=0.04) all decreased.</td>
<td>Children on peritoneal dialysis (N=7)</td>
<td>11.5 g/dl (target 10.5-12.0 g/dl)</td>
<td>6.9 g/dl</td>
<td>Level 2+</td>
</tr>
</tbody>
</table>
There was no change in shortening fraction, interventricular septum and left ventricular posterior wall thickness. No change was found in systolic, diastolic or mean BP.

<table>
<thead>
<tr>
<th>Study</th>
<th>Exercise testing and quality of life</th>
<th>Patient population (N)</th>
<th>Achieved high Hb</th>
<th>Achieved low Hb</th>
<th>Evidence grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>241</td>
<td>No changes were found in the 2-minute walking distance (N=7) and treadmill exercise testing workload (N=3). A reduction in heart rate at rest was found after epoetin administration (P=0.02) and at each successive stage of the exercise test. No arrhythmias or ischaemic changes were found.</td>
<td>Children on peritoneal dialysis (N=7)</td>
<td>Median 11.2 g/dl (range 9.5-14.2 g/dl)</td>
<td>Median 7.3 g/l (range 4.2-8.1 g/l)</td>
<td>Level 2+</td>
</tr>
<tr>
<td>241</td>
<td>Quality of life (25-part parental questionnaire, using a visual analogue scale) found an improvement</td>
<td>Children on peritoneal dialysis (N=7)</td>
<td>Median 11.2 g/dl (range 9.5-14.2 g/dl)</td>
<td>Median 7.3 g/l (range 4.2-8.1 g/l)</td>
<td>Level 2+</td>
</tr>
</tbody>
</table>
6.10.3 From Evidence to Recommendations

6.10.3.1 The use of exercise testing for outcomes in the Morris papers is not meaningful in very young children, which exacerbates the problem of the small sample. Recommendations pertaining to children with anaemia of chronic kidney disease are presented in relevant sections throughout the guideline.

6.11 Adjusting ESA Treatment

6.11.1 Clinical Introduction

6.11.1.1 ESA dose adjustments are made to encourage haemoglobin levels into the recommended ranges. The details of such ‘targeting’ varies unit by unit, but must always involve decisions on when to make the dose change (i.e. at what haemoglobin level), and by how much to change the ESA dose and/or frequency. ESA treatment (even with the currently available long-acting agent) involves delivery of short, intermittent, pharmacological bursts of bioavailable EPO which bear no relation, either temporally or in magnitude, to normal physiological control of erythropoiesis. Under normal conditions, the body’s oxygen sensing, EPO-producing, and erythropoietic systems are closely regulated and coordinated to maintain haemoglobin levels within a narrow range. During ESA treatment haemoglobin levels fluctuate widely and the pattern of fluctuation varies from patient to patient. This haemoglobin cycling may complicate the management of anaemia associated with CKD. Factors likely to be associated with fluctuations in haemoglobin level include changes in ESA dose, intravenous iron treatment, intercurrent illness (especially infection) and hospitalisation. Those patients experiencing more frequent fluctuations, and those with the greatest amplitude of fluctuation, have been characterised as being more responsive to ESAs.

| physical performance and general health (P<0.02), but the global score did not find an improvement in quality of life |  |  |  |
the haemoglobin level falls above or below these limits. The extent of the dose change, whether an absolute amount or a proportion of the existing dose, has to fit the available ESA formulations or decisions are required about the dosage interval. However, because of logistical delays in responding to any current laboratory value and because of differences in the momentum of haemoglobin change it may be necessary to alter ESA treatment pre-emptively prior to the haemoglobin level breaching the limits of the desirable range. There are also individual variations in the response to ESA that may be taken into account from historical data. The case mix and treatment history of any patient cohort will also influence outcome and whilst tailoring of the timing and dose changes may be attempted there is inevitable unpredictability of outcome.

6.11.1.3 So how then do we adjust ESA dose and dose frequency to keep haemoglobin levels within the maintenance range, and what factors determine how we do this?

6.11.2 Clinical Methodological Introduction

6.11.2.1 A literature search found thirteen studies - an RCT, prospective cohort studies, retrospective cohort studies, cross-over studies, retrospective longitudinal studies, and cross-sectional studies.

6.11.2.2 One study had methodological limitations and was therefore excluded from the evidence statements.

6.11.3 Clinical Evidence Statements

Factors affecting epoetin dose

Route of epoetin administration

Haemodialysis Patients

6.11.3.1 One study, found patients administered with epoetin by the i.v. route received significantly higher doses than those prescribed epoetin by the s.c. route (P=0.0001).

Level 3

Iron status

Haemodialysis patients

6.11.3.2 Three studies found epoetin dose to be inversely correlated with iron status when measured by means of serum transferrin saturation (P=0.0001), serum
saturation ratio \( r=-0.16, P=0.003 \) \(^{255}\) and total iron binding capacity levels \( r=0.27, P<0.01 \) \(^{250}\).

**Level 3 and Level 2+**

6.11.3.3 In contrast, one study \(^{250}\) did not find an association with serum transferrin saturation. Also, no association between erythropoietin dose and serum ferritin levels was found in two studies \(^{253,250}\).

**Level 3 and Level 2+**

**Dialysis adequacy**

**Haemodialysis patients**

6.11.3.4 One study \(^{253}\) found an inverse correlation between urea reduction ratio and administered erythropoietin dose \( P<0.0001 \).

**Level 3**

**Cause of End-Stage Renal Failure (ESRD)**

**Haemodialysis patients**

6.11.3.5 One study \(^{253}\) found diabetes mellitus as the cause of ESRD to be associated with lower erythropoietin doses \( P=0.003 \).

**Level 3**

**Inflammation**

**Haemodialysis Patients**

6.11.3.6 One study \(^{255}\) found a direct correlation between administered erythropoietin dose and malnutrition-inflammation score (i.e. increasing degree of severity) \( r=+0.13, P=0.03 \). This was reflected in the direct correlation between weekly erythropoietin dose and logarithmic inflammatory cytokines, IL-6 \( r=+0.31, P<0.001 \) and TNF-\( \alpha \) \( r=+0.18,0.001 \) as well as C-reactive protein \( r=+0.18, P<0.001 \) and lactase \( P<0.001 \) levels. Similarly, there was an inverse correlation observed between erythropoietin dose and nutritional markers \( r=-0.19, P<0.001 \).

6.11.3.7 In another study \(^{256}\), albumin \( R=-0.359, P<0.001 \), log CRP \( R=0.337, P=0.001 \), log ferritin \( R=0.240, P=0.021 \) and transferrin \( R=-0.264, P=0.011 \) all showed correlation with erythropoietin/Hct ratio. When patients in the lowest and highest erythropoietin/Hct quartiles were compared, only median CRP showed statistical significance \( P=0.009 \).

**Level 3**

6.11.3.8 Contrary to the above findings, in one study \(^{257}\), C-reactive protein levels did not show any association with erythropoietin dose.

**Level 3**

**Peritoneal dialysis patients**
6.11.3.9 In one study, albumin (R=-0.453, P=0.006) and CRP (R=0.375, P=0.024) showed correlation with epoetin/Hct ratio, but not ferritin.

**Level 3**

*Haemodialysis vs. peritoneal dialysis patients*

6.11.3.10 When compared to each other in the same study, haemodialysis patients had a greater epoetin/Hct ratio than peritoneal dialysis patients (P<0.001), which was matched with a higher epoetin dose (P<0.001) and lower Hct levels (P=0.002). Also lower CRP (P<0.001), ferritin (P<0.001), transferrin (P<0.001) and aluminium (P<0.001) levels were found in the haemodialysis patients. However, no difference was observed for albumin, transferrin saturation, intact parathyroid hormone and PCRn.

**Level 3**

*Adjunctive medical treatment*

*Haemodialysis patients*

6.11.3.11 Higher epoetin doses were administered to patients receiving ACE-inhibitor therapy when compared to those not treated with ACE-inhibitors (P<0.05) in one study. In a 12-month study, patients receiving high dose enalapril (ACE-inhibitor) required a higher epoetin dose at the end of the study period (P<0.0001) and also when compared to those receiving nifedipine (calcium channel blocker) (P<0.0001) or control (epoetin only) (P<0.0001) to maintain a Hb >10 g/dL. Similarly, in a 12 month study aimed to maintain Hb >10 g/dL, high dose losartan (angiotensin II receptor blocker) required a higher epoetin dose at the end of the study period (P<0.0001) and also when compared to those receiving amlodipine (calcium channel blocker) (P<0.0001) or control (epoetin only) (P<0.0001).

**Level 2+**

6.11.3.12 In contrast to the above findings, two studies with patients receiving ACE-inhibitors aimed to maintain Hct levels at 30-36% (Hb ~10-12 g/dL), did not find any association between ACE-inhibitor administration and epoetin resistance.

**Level 2+**
**Peritoneal dialysis patients**

6.11.3.13 Weekly epoetin dose given to maintain Hct >30% (Hb ~ 10 g/dL) at the end of a 12 week study was greater in patients receiving ACE-inhibitor (P<0.01) and in patients receiving angiotensin II receptor blocker treatment (P<0.05), but not in those receiving calcium channel blockers when compared to individual weekly doses at the beginning of the study. In addition, plasma epoetin levels were higher in the ACE-inhibitor treated group (P<0.05) but not in the angiotensin II receptor blocker and control groups.

**Level 1+**

**Parathyroid hormone**

**Haemodialysis patients**

6.11.3.14 In a study conducted in patients over the age of 65 years, whereby patients were divided into PTH >250 pg/ml and <250 pg/ml, despite similar epoetin doses and serum iron and ferritin levels, patients in the hyperparathyroid group had lower Hb and Hct levels (P=0.009 and P=0.008 respectively) as well as higher levels of alkaline phosphatase (P=0.023), phosphorous (P=0.001) and calcium x phosphorous product (P=0.009).

**Level 2+**

**Hospitalisation**

**Haemodialysis patients**

6.11.3.15 In one study, higher epoetin doses were required in patients who were transfused during hospitalisation up to 2 months following discharge (P<0.05).

**Level 3**

6.11.3.16 The same study found no association between discharge diagnosis, (inflammatory vs. non-inflammatory) or surgical procedure during hospitalisation and epoetin requirement up to 2 months following discharge.

**Level 3**

**Dialysate chloramine levels**

**Haemodialysis patients**

6.11.3.17 One before and after study (N=72) found an association between higher achieved Hb level (P<0.001) and decreased epoetin dose (P<0.001) with installation of new carbon filters, which decreased the chloramine levels from to 0.25 ppm to <0.1 ppm. This was supported by findings in a sub-group analysis (N=15) that showed low-grade haemolysis by a post-dialysis rise in
methaemoglobins (P<0.01) and a drop in haptoglobins (P<0.01), which was not detected after the use of the carbon filters. Additionally, the water board confirmed the sustained 2-fold increase in chloramines levels and acceptable levels of nitrate, aluminium, bacterial counts and endotoxins in the mains water supply during the study time period. In agreement, one satellite dialysis unit, \(^{249}\) found decreasing Hb levels at months 10 (P<0.01) and 11 (P<0.01) of the study despite higher epoetin dose (P=0.04) when compared to other local dialysis units. These findings were associated with a high chlorine water content relative to the desirable limit (P not given), which coincided with evidence of haemolysis as shown by higher ferritin (P<0.01) and low haptoglobin (P value not given). Furthermore, installation of an activated charcoal filter decreased chlorine concentration to <0.02, which was accompanied by an increase in Hb and a reduction in epoetin requirement.

**Level 2+ and Level 3**

6.11.4 Health Economics Methodological Introduction

6.11.4.1 The appraised study performed a decision analysis comparing three dosage regimens: strategy-6, 6000U (107U/kg), epoetin-9 strategy, 9000U (167 U/kg) and epoetin-12 strategy, 12,000U (211 U/kg) of subcutaneous epoetin in continuous ambulatory peritoneal dialysis to maintain the target Hct level of 0.33 (equivalent to 11g/dL) \(^{259}\). Epoetin was given weekly for the first 2 months until a target Hct of 0.33 was reached. This was maintained for an additional 3 months with the administration frequency reduced to fortnightly or 4-weekly. Non-responders in 6000U and 9000U after 2 months entered 12,000 U regimen.

6.11.5 Health Economics Evidence Statements

6.11.5.1 Of the three subcutaneous epoetin strategies compared, it was most cost-effective in peritoneal dialysis patients to give 6000 units weekly for 2 months, followed by a weekly or 2-weekly epoetin 6000 unit dose for the next 3 months while maintaining the target HCT level of 0.33 and to restart non-responders after 2 months on the 12,000 unit epoetin strategy. \(^{259}\) The savings from the lower administration frequency reduced to fortnightly or 4-weekly. Non-responders in 6000U and 9000U after 2 months entered 12,000 U regimen.

6.11.5.2 Varying the parameters over the 20-week treatment period:
- Epoetin-6 strategy is always the least costly over $0-60 range for drug administration costs. Drug administration costs must be $137 for Epoetin-6 to become more costly than Epoetin-12.
- Epoetin-6 is least costly over the 95% CI range for response probabilities.
- Epoetin-12 strategy becomes less costly than the Epoetin-9 as drug administration costs increase over $35.

6.11.5.3 Varying the parameters over a 1-year treatment period:
- Epoetin-6 was less costly than both Epoetin-9 and Epoetin-12 over range of costs ($0-60).
- Epoetin-6 becomes more costly than Epoetin-12 at $95.
- Epoetin-6 less costly over whole range of 95% CI.
- Epoetin-9 was more costly than Epoetin-12 at lower 95% CI limit.
- Epoetin-12 becomes less costly than Epoetin-9 at drug administration costs of $8 per injection and above.

6.11.6 From Evidence to Recommendations

6.11.6.1 Of all of the outcomes considered in the evidence the GDG felt that the route of ESA administration, the patients iron status, administration of adjunctive medical treatment, and the presence or absence of inflammation were of most relevance to determine the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range in all CKD patients. Dose adjustments were also likely to be influenced by:

- the patients haemoglobin level
- the observed rate of change in haemoglobin level
- by an individual patients response to ESA treatment.

6.11.6.2 In patients on haemodialysis, chloramine levels in dialysis water were also of relevance. The outcomes of dialysis adequacy, adjunctive medical treatment, race, and parathyroid hormone levels were discussed but the evidence was either limited or would be more fully covered in separate guideline sections, the GDG therefore did not wish to make any recommendations regarding these. The outcomes of end-stage renal failure and hospitalisation were included but the GDG did not feel that they were helpful in determining the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range for individual patients.

6.11.6.3 With regards to the route of administration, two studies reported that dose of short-acting ESAs could be reduced when administered subcutaneously (s.c.) as opposed to intravenously (i.v.) [192;444]. It was noted that in the UK epoetin alpha is not currently licensed for subcutaneous use but this may alter in the future. It was also noted that the decision of whether to administer ESAs s.c. or i.v. was also a matter of patient choice.

6.11.6.4 Several studies supported the view that the amount of ESA required is inversely correlated with iron status [192;444;395]. The GDG felt this was an important factor to take into account when determining the dose and frequency of ESA required to keep haemoglobin levels within the maintenance range and also Unit policy in view of the need for uniform and convenient clinical procedures.
6.11.6.5 The GDG noted that there was evidence to support a correlation between the weekly dose administration of ESA and inflammatory cytokines (IL-6, TNF-alpha).

6.11.6.6 The GDG noted that the evidence supported the intuitive notion that sicker patients generally require higher doses of ESAs. The GDG discussed that intercurrent illness may be a cause of temporary resistance that should be assessed, and it was noted that in patients with a chronic illness, resistance to ESAs may be prolonged.

6.11.6.7 The GDG discussed the evidence with respect to adjunctive medical treatment, that patients receiving either ACE inhibitor therapy or angiotensin type II receptor antagonists required an increased dose of ESA in comparison to those patients administered a calcium channel blocker or to control groups. Two further studies reported no association between ACE-inhibitor administration and resistance to ESAs. The GDG considered one study to have methodological limitations due to the non-randomised study design. The GDG noted that the treatment ranges in these studies were appropriate and the doses being administered would not lead the GDG to consider that ESA resistance should be suspected. The GDG concluded that there was no evidence that ACE-inhibitors caused ESA resistance and that such treatment should not be stopped, although the dose of ESA may require adjustment.

6.11.6.8 The GDG discussed the implications of dialysis water purity on ESA administration, in particular the GDG noted that increased chloramines (formed by the combination of free chlorine and ammonia gas) levels were associated with a need for higher doses of ESAs in haemodialysis patients. The GDG discussed that the addition of activated charcoal filters reduced the level of chlorine in the dialysis water. However, it was noted that these filters can be prone to infection suggesting that a risk-benefit analysis would be useful. It was noted that neither study had performed such an analysis. The GDG noted that NHS Estates have produced a document covering facilities for renal services. This outlines that the required standards for water purity must be monitored and achieved and specifically notes that ‘carbon filters should be selected to achieve sufficient contact time to remove all chlorine and chloramines’.

6.11.6.9 The GDG discussed monitoring issues around how frequently patients should be monitored and when to intervene to correct the Hb level. It was felt that there was a need to follow the trend of a patients response to Hb but that in general it was
felt that if two consecutive tests taken a month apart fell outside the target range, or if the rate of rise or fall of haemoglobin exceeded 1 g/dL/month then intervention would be necessary to correct the Hb level.

6.11.6.10 With regards to the health economic evidence, the GDG felt that there were some issues with the transferability of the costs from a study conducted in the USA to the UK health care setting. However, the GDG did agree with the principal message that giving a low-dose of ESA more frequently was more cost-effective at the Unit level.

6.11.7 Recommendations

6.11.7.1 In patients with anaemia of chronic kidney disease, iron status should be optimised before or coincident with the initiation of erythropoietin administration. (C)

6.11.7.2 In patients with anaemia of chronic kidney disease, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor antagonists is not precluded but may necessitate an increase in ESA therapy. (D)

6.11.7.3 In patients with anaemia of chronic kidney disease the haemoglobin measurements should be taken into account when determining the dose and frequency of erythropoietin administration: (D(GPP))

- The cause of an unexpected change in Hb level should be investigated (i.e. intercurrent illness; bleeding) to enable intervention
- ESA dose and/or frequency should be increased or decreased when Hb measurements fall outside action thresholds (usually below 11.0g/dL or above 12.0g/dL), or for example when the rate of change of haemoglobin suggests an established trend (e.g. >1g/dL/month)

6.12 Treating Functional Iron Deficiency: correction

6.12.1 Clinical Introduction

6.12.1.1 Whilst there are many different preparations of oral iron available (Table) there are currently only two forms of parenteral iron licensed in the UK, iron sucrose and iron dextran. The key issues are iron safety and efficacy.
Table 40: Iron content of different oral iron preparations

<table>
<thead>
<tr>
<th>Iron salt</th>
<th>Dose</th>
<th>Content of ferrous iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>100 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulphate, dried</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>

6.12.1.2 Oral iron preparations contain varying amounts of ferrous iron, the frequency of gastrointestinal side effects related to each different preparation tends to be directly related to the content of ferrous iron. Common adverse effects from oral preparations include constipation, diarrhoea, nausea, vomiting, and dyspepsia.

6.12.1.3 Iron sucrose is a complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron and iron dextran is a complex of ferric hydroxide with dextran containing 5% (50 mg/mL) of iron. Adverse effects from intravenous iron are mainly related to the size of dose and rate of infusion. Potential adverse effects include nausea, vomiting, abdominal pain; flushing, anaphylactoid reactions, dyspnoea, numbness, fever, urticaria, rash, arthralgia, myalgia; blurred vision; injection-site reactions including phlebitis; rarely diarrhoea, arrhythmias, hypotension, chest pain, seizures, tremor, dizziness, fatigue, sweating.

6.12.1.4 Intestinal iron absorption declines as serum ferritin increases\(^{261,262}\) and ESA administration boosts iron absorption in erythropoietin deficient haemodialysis patients\(^ {263}\). Patients with CKD who have anaemia, a GFR below 40 mL/min, and are not receiving ESA treatment are likely to be erythropoietin deficient\(^ {100}\), the relative lack of oral iron efficacy in each of these conditions may be due to a lack of erythropoietin-stimulated iron absorption. This lack of oral iron efficacy led to the use of intravenous iron and early use of IV iron employed low doses given relatively frequently and administered as an infusion. Frequent administration of IV iron in haemodialysis patients is made feasible through use of dialysis vascular access but in peritoneal dialysis and pre-dialysis patients venous access is required for each dose. Administration of higher doses in CKD patients not on haemodialysis offers the potential to spare time and venous access, but at the possible expense of increased adverse effects.

6.12.1.5 Relative to other CKD patient groups there is a wealth of information concerning iron status and response to iron administration in patients on haemodialysis. In
CKD patients not on dialysis low iron indices are common. TSAT levels below 20% and ferritin levels below 100 µg/L may occur in up to 20-70% of patients, depending on CKD stage and gender. However, little is known about the relationship between baseline iron status, the likelihood of a response to an iron challenge, and the relative efficacy and safety of oral versus intravenous iron.

6.12.1.6 Iron therapy in haemodialysis patients is an essential adjuvant to ESA treatment and adequate iron stores are required prior to treatment with ESAs to ensure effective erythropoiesis. Virtually all haemodialysis patients will require ESA treatment to achieve target haemoglobin levels. By contrast, a significant proportion of pre-dialysis CKD patients, and some peritoneal dialysis patients, may not require ESA therapy to achieve target haemoglobin levels. Iron therapy in these patients may be undertaken as primary treatment of anaemia.

6.12.2 Methodological Introduction

6.12.2.1 A comprehensive literature search identified one RCT investigating the efficacy of oral vs. IV iron in pre-dialysis patients with or without concurrent ESA therapy and two before and after studies investigating the efficacy of IV iron over 6 months or as a single dose in iron deficient predialysis patients who had not previously received ESA therapy.

6.12.2.2 One study did not meet quality criteria and was therefore excluded from the evidence statements.

6.12.3 Evidence Statements

Iron dextran: Predialysis patients

6.12.3.1 Following administration of 1g iron dextran in 500 ml normal saline IV as a total dose infusion over 6 hours (N=56), Hb (P<0.001) and serum ferritin (P<0.0001) levels increased after 12 weeks. However, this increase in Hb was not apparent after one year (N=21), ferritin was still increased compared to baseline, although to a lesser extent than at 12 weeks (P<0.001). In addition, no major adverse events were found and systolic and diastolic BP did not change after 12 weeks.

Level 3

Ferric saccharate (also known as ferric hydroxide sucrose or iron sucrose): Predialysis patients
6.12.3.2 In one study 200 mg elemental iron (Ferric saccharate) was administered in 150 ml saline over 2 hours, once monthly for 5 months, to give a total IV iron dose of 1,000 mg per patient (N=33). After 3 months of IV iron treatment, the mean Hct and Hb values were not significantly increased, despite raised serum ferritin levels compared to baseline (P<0.05). At 6 months, however (i.e. 1 month after the last iron dose), the mean Hct (P=0.035) and Hb (P=0.008) had significantly increased. Additionally, there were no differences in those responding to IV iron treatment with an increase in mean Hct and Hb compared with those not responding in any of the other parameters (serum creatinine, creatinine clearance, systolic and diastolic BP) either before or after onset of IV iron therapy. None of the patients reported side effects during the study period. Also, no correlation was found between Hb/Hct and any other of the study parameters in the responders and non-responders.

Level 3

Oral vs. IV iron sucrose: Predialysis patients

6.12.3.3 In a RCT investigating IV iron sucrose 1,000mg in divided doses over 14 days administered either as an injection or infusion vs. oral ferrous sulphate 325 mg three times daily (≈ 195 mg ferrous iron per day) for 56 days, in patients with and without ESA use, mean adherence of 97.3 (95% CI 94.3-100.0) in the IV treatment group was greater than in the oral treatment group mean 88.5 (95% CI 84.8-92.3). In addition, both the proportion of patients who achieved the primary end point (i.e. rise in Hb ≥ 1.0 g/dl) (P=0.0344) and the mean increase in Hb were higher in the IV group by day 42 (P=0.0298). Notably, the difference in ESA use in achieving primary end point in the IV and oral group was not found to be significant. 3 patients in the IV group discontinued treatment due to adverse events attributed to the study drug (hypotension, n=2 and nausea, n=1). Transient taste disturbance (dysgeusia) was the most prominent GI complaint associated with IV iron administration. Constipation, diarrhoea, nausea, vomiting and dyspepsia were associated prominently with oral iron therapy, whilst headache, myalgia and hypotension were exclusively associated with IV iron administration.

Level 1++

6.12.4 Health Economics Methodological Introduction

6.12.4.1 One study was found but did not meet quality criteria. The patient population contained three patients receiving epoetin, methodology of analysis was not stated, cost analysis was insufficiently reported and there was no estimation of uncertainty.

6.12.5 From Evidence to Recommendations

6.12.5.1 The available published evidence does not suggest the most effective and safest dose, frequency, preparation or route of administration of iron in ACKD patients.
with functional iron deficiency prior to ESA treatment. GDG consensus was that patients with anaemia associated with CKD and functional iron deficiency will require intravenous iron treatment. The published evidence did not allow the GDG to recommend a preparation. Two preparations are available in the UK and the dose and frequency will be dictated by the preparation used and by measurement and monitoring of iron indices (serum ferritin and %HRC or %TSAT).

6.12.6 Recommendations

6.12.6.1 Following a tolerated test dose, people with anaemia of chronic kidney disease who are receiving ESAs and are not iron replete (i.e. functional or absolute iron deficiency) should be given a loading dose of iron. Most patients will require 600-1000mg for adults or equivalent doses for children, in single or divided dose depending on the preparation. Iron treatment should be managed to maintain target ranges of: (D(GPP))

- serum ferritin > 150 ug/l
- transferrin saturation > 20% (unless ferritin > 800ug/L)
- hypochromic red blood cells < 6% (unless ferritin > 800 ug/L)

Patients with functional iron deficiency should be treated with intravenous iron.

See 3.2.2 for the associated algorithm

6.13 Treating Functional Iron Deficiency: maintenance

6.13.1 Clinical Introduction

See 6.12.1.

6.13.2 Methodological Introduction

6.13.2.1 Due to the high number of retrieved studies in the literature search, these were grouped into:

- induction iron therapy for iron deficient (both absolute and functional iron deficiency) and
- maintenance iron therapy for iron replete patients on epoetin

and thereafter further subgrouped into the various iron routes and frequencies of administration investigated. The seventeen studies to be included in the evidence statements were selected on the basis of evidence level hierarchy.
6.13.2.2 Two studies did not meet quality criteria and was therefore excluded from the evidence statements.

6.13.2.3 Of note:
- Three studies were conducted in children.
- Study durations ranged from 12 weeks to 18 months, which has implications on the time required to measure stability of treatment outcomes.

6.13.2.4 The GDG agreed that the following outcomes were priorities:
- Epoetin dose
- Efficacy/Hb response
- Compliance
- Patient preference
- Side effects
- Safety - cardiovascular
6.13.3 Evidence Statements

**Oral iron vs. Intravenous Iron**

Two RCTs \(^{274,275}\) in adult dialysis patients with serum ferritin levels >100 µg/L compared IV and oral iron. One study \(^{274}\) (n=52, all haemodialysis) administered 100 mg IV iron dextran twice a week and the other \(^{275}\) (n=37, 15 haemodialysis and 19 peritoneal dialysis) administered 250 mg iron dextran fortnightly. Oral comparators were ferrous sulphate (200-325 mg tds) and iron polysaccharide (150 mg bd). Both studies found IV iron to be superior, in one study \(^{274}\) haematocrit increased (p<0.05) and ESA dose fell (p<0.05), in the second study \(^{275}\) haemoglobin increased (p<0.05) compared to those treated with oral iron.

**Level 1+**

A study in pre-dialysis patients \(^{276}\) randomised patients with baseline ferritin levels of 47-155 µg/L to either oral ferrous sulphate 200 mg tds (n=23) or 300 mg intravenous iron sucrose. Over a follow up period of 5.2 months no difference in haemoglobin level or ESA requirement was observed.

**Level 1++**

In a 29 day study with follow-up after 14 days \(^{277}\) patients were randomised to epoetin and intermittent IV iron sucrose 200 mg bolus weekly (N=48) vs. epoetin and ferrous sulphate (65 mg elemental iron) orally 3 times daily (N=48). Although the IV iron group had a greater increase in serum ferritin levels (P<0.0001), the rise in Hb from baseline was not statistically different between the 2 treatment groups. However, when patients were stratified by a baseline serum ferritin < or ≥100 µg/L, the IV iron group had a greater increase in Hb at follow-up compared to oral iron patients (P<0.05). Also, more patients in the IV iron group attained Hb >11.0 g/dl compared to the oral iron group (P=0.028) and the % change from baseline to follow-up for both Hb and ferritin was significantly greater for the IV iron group (P<0.0001). Mean treatment concordance, assessed by tablet counts was lower in the oral iron group (85.5%) compared with the IV iron group (95.0%) - no P value reported. GI side effects were more common in the oral iron group and taste disturbances in the IV iron group. No patient required discontinuation of iron treatment in either group.

**Level 1+**

In a study conducted in peritoneal dialysis patients \(^{278}\) comparing oral and intravenous iron using a crossover design higher haematocrit levels (P=0.02) and lower ESA doses (P=0.008) were found with intravenous iron. Nine patients received oral ferrous sulphate 325 mg tds for 4 months followed by a single bolus infusion of 1 g iron dextran after a washout period of one month.

**Level 2+**

One study conducted in children with %TSAT>20 \(^{271}\) randomised them to intravenous iron dextran or oral ferrous fumarate (n=35, all haemodialysis). Doses were based on weight; ferrous fumarate varied between 4-6 mg/kg/day, children <20 kg received 25
mg/week iron dextran, those weighing 20-40 kg received 50 mg/week and those >40 kg received 100 mg/week. After 16 weeks no differences in ESA requirements or haemoglobin levels were found.

**Level 1+**

*Intravenous iron studies in adults*

Three observational studies in haemodialysis patients noted a reduction in ESA requirements with regular maintenance intravenous iron (P<0.0005)\(^{279}\), (P<0.05)\(^{280}\), (P<0.001)\(^{281}\). One study\(^ {279}\) (n=116) used iron sucrose 100 mg post-haemodialysis. Another study\(^ {280}\) (n=24) used either a loading dose of 1g iron dextran given in divided doses over 10 consecutive dialyses followed by further boluses when %TSAT fell below 20 or serum ferritin fell below 200 µg/L; or an initial pulse of iron dextran 300-500 mg followed by 25-100 mg every 1-2 weeks to maintain %TSAT 30-50. The third study\(^ {282}\) (n=396) maintained haemoglobin at a median level of 11.3 to 11.8 g/dl over a 24 month period. Patients with serum ferritin <500 µg/L were treated with concomitant IV iron sucrose regimen as follows: months 1-3, for ferritin <100 µg/L, 50 mg iron sucrose twice weekly; for ferritin 100-500 µg/L, 50 mg iron sucrose once weekly; months 4-9, for ferritin <100 µg/L, 50 mg iron sucrose twice weekly; for ferritin 100-500 ng/ml, iron sucrose dose depended on functional iron deficiency. Those with %HRC <5% were given 50 mg iron sucrose once weekly and those with %HRC >5%, 50 mg iron sucrose twice weekly. During months 10-24 those with ferritin <100 µg/L received 50 mg iron sucrose thrice weekly. Those with ferritin 100-500 µg/L received 50 mg iron sucrose once weekly if %HRC <2% (iron replete), or 50 mg iron sucrose twice weekly if %HRC 2-5%, or 50 mg iron sucrose thrice weekly if %HRC >5%.

**Level 2+ and Level 3**

Another observational study in haemodialysis patients\(^ {283}\) stratified patients’ response to 20 mg intravenous iron saccharate given 3 times/week over a 6 month period by ferritin <100 µg/L (n=17) versus ≥100<400 µg/L (n=16). Haemoglobin levels (p<0.0001) increased and ESA levels decreased (p<0.003) in all patients compared to baseline but there was no difference between groups. 4 patients reported a metallic taste in association with iron but no other adverse events were reported.

**Level 2+**

A further observational study\(^ {284}\) administered 100 mg intravenous ferric saccharate twice a month to 41 haemodialysis patients and 4 peritoneal dialysis patients who had been receiving ESAs for at least 6 months, and 11 haemodialysis patients who started ESA and intravenous iron simultaneously. In those previously on ESA, haematocrit levels were higher (p<0.05) and ESA doses lower (p<0.05) after 12 months. Those who started ESA and intravenous iron simultaneously had higher haematocrit levels (P<0.05) after 6 months of treatment.

**Level 2+**

Four studies compared different intravenous iron dosing regimens\(^ {285}\),\(^ {286}\),\(^ {287}\),\(^ {288}\). In 3 studies conducted in haemodialysis patients the same total dose of iron was administered. One study\(^ {285}\) gave 400 mg saccharated ferric oxide in 10 divided doses either following 10 consecutive dialysis sessions (n=12) or weekly for 10 weeks (n=12).
This study also included 11 subjects to whom iron was not administered. These patients had lower haemoglobin levels and greater ESA requirements compared to the iron-treated groups. The only difference in the iron treated groups was a lower ESA requirement compared to baseline (p<0.01) in those given sequential treatment after each dialysis. One study gave a total of either 600 mg iron dextran (n=43). Patients received either a single bolus dose, 6 divided doses of 100 mg following consecutive dialyses, or 100 mg/week for 6 weeks. No difference in haemoglobin or ESA requirements with the different dosing regimens.

**Level 1+ and Level 2+**

A further study in haemodialysis patients aiming for a target haemoglobin level of 11.8 g/dL compared 3 different iron dextran regimens. A total dose infusion of 550-2000 mg was used in 14 patients, 12 patients received 500 mg/week as a bolus dose to a total of 400-1500 mg and 17 patients were given 100 mg/dialysis session to a total dose of 500-2100 mg. No differences in peak haematocrit or time to peak haematocrit were observed between groups.

**Level 1+**

In peritoneal dialysis patients one study gave a total dose of intravenous ferric saccharate of 600 mg in divided doses with 2 different regimens using a crossover design (n=17). There was a greater increase in haematocrit levels in patients given 50 mg twice a week (P<0.05) compared to those given 100 mg/week.

**Level 1+**

*Intravenous iron studies in children*

In a 6 month study (n=40) children <16 years of age received Epoetin to target Hct ≥30%. IV iron dextran administered as a maintenance dose of 1mg/kg/week following a weight-based loading dose was compared with an as required intermittent weight based course of 10 doses of iron dextran if Hct was <33%, ferritin <100 µg/L and/or TSAT <20%. Despite the higher cumulative dose in the intermittent group (P<0.001) the average Epoetin dose was similar in both groups and Hb increased to 10 g/dl, with no difference between the 2 treatment groups.

**Level 1+**

A double-blind RCT study in children <16 years old receiving Epoetin\textsuperscript{273} randomised patients to concomitant treatment with 8 consecutive intravenous infusions of either 1.5mg/kg (N=24) or 3.0 mg/kg (N=32) of sodium ferric gluconate complex. Mean cumulative dose in the 1.5 mg/kg group was 431 ± 168 mg and 725 ± 202 mg in the 3.0 mg/kg group (P<0.0001). Although increases from baseline were found in both groups at 2- and 4-week evaluation time points after the last iron dose, no difference was found in Hb levels between the two groups. Responders were defined by Hb increase ≥1.0 g/dl. No difference was found between number of responders in either group. Epoetin dose remained unchanged in both treatment groups.

**Level 1+**

*Intravenous iron safety studies*
In a safety study, N=657 patients received 200 mg bolus injections of iron sucrose\(^\text{289}\). A total of 2,297 injections were administered, with some patients receiving multiple injections with a minimum of 1 week between injections. Mild and transient metallic taste was found for 412 injections and other adverse events for 57 injections. These were anaphylactoid reactions in N=7 patients; pain during injection in N=31 patients; pain after injection in N=9 patients, with/without bruising; nausea/GI symptoms in N=3 patients; lethargy in N=4 patients; and light-headedness in N=3 patients.

**Level 3**

A cohort study\(^\text{290}\) (n=32,566) sought to investigate if an apparent relationship between iron dosing and mortality was confounded by incomplete representation of iron dosing and morbidity over time. The study found doses of iron >1,000 mg over 6 months to be associated with increased risk of mortality compared to subjects not receiving iron using an adjusted proportional hazards analysis relating baseline iron dose to survival with a hazard ratio (HR) of 1.09 (95\% CI 1.01-1.17). Those receiving >1800 mg of iron had HR 1.18 (95\% CI 1.09-1.27). However, the association disappeared when the adjusted probability of dying in a particular month as a function of cumulative iron dose received during the previous (i) 0 to 6 months (ii) 6 to 12 months and (iii) 12 to 18 months was estimated. No significant association was found between mortality and any level of iron dosing >0 to >1800 mg over 6 months.

**Level 2+**

**Oral Iron Studies**

One study\(^\text{291}\) randomised iron replete patients to polysaccharide-iron complex 150 mg elemental iron twice daily (N=12) vs. placebo (N=13) over 3 months with 2 months follow-up. No difference was found in Hct levels between the 2 groups. The same study also randomised iron deficient patients to either polysaccharide-iron complex 150 mg elemental iron twice daily (N=14) or placebo (N=10) over 3 months and 2 months follow-up. Those receiving iron had an increase in Hct levels (P<0.01)

**Level 1+**

Another study\(^\text{292}\) randomised patients to a number of different oral iron preparations containing a daily dose of 200 mg elemental iron, ferrous fumarate (Chromagen, n=12 and Tabron, n=11), ferrous sulphate (n=11) and iron-polysaccharide complex (n=12). Patients were also given various doses of daily ascorbic acid (750, 1,000, 0, 100 mg respectively) over 6 months. Hct levels increased with all preparations (Chromagen and ferrous sulphate, P<0.01; Tabron P<0.05), except for the iron-polysaccharide complex. In addition, Hct/Epoetin ratio decreased (P<0.05) in the Tabron (ferrous fumarate) treatment group only. No differences were noted in compliance.

**Level 1+**

**6.13.4 Health Economics Methodological Introduction**

**6.13.4.1** Six studies were appraised\(^{293,294,295,296,297,298}\) and one study met quality criteria\(^{293}\). Three of the studies did not report unit costs, total costs or doses adequately\(^{294,295,297}\). One study was excluded due to potential bias by physician adjustment of
the epoetin dose in a before and after design\textsuperscript{296}. Study\textsuperscript{298} was excluded as cost-
savings were not based on evidence.

6.13.5 Health Economics Evidence Statements

6.13.5.1 One study found iron dextran did not reduce the average dose of EPO in 33
patients but improved the number of patients with ‘successful treatment’ (10 vs.
27). Successful treatment was defined as a haematocrit of 33-36%, transferrin
saturation of >20%, ferritin concentration of >100ng/mL and no blood administered
except for acute blood loss. The study estimated the incremental cost-
effectiveness of iron dextran to be $41.61 (US$, 1998) per successful treatment
\textsuperscript{293}. No sensitivity analysis was performed.

6.13.6 From Evidence to Recommendations

The published evidence was very limited in peritoneal dialysis and pre-dialysis patients.
It did not provide data to allow the GDG to specify a test dose of iron in the
recommendations, nor a route or frequency of administration.

6.13.6.1 Caution may be required due to the potential side-effect profile (particularly
anaphylaxis) when administering both test and maintenance doses of iron.

6.13.6.2 The GDG acknowledged the cost-effectiveness evidence of pre-dialysis anaemia
treatments is limited as there is little data to make comparisons to alternative
treatments and insufficient effectiveness data of patient benefit such as quality of
life. The GDG noted that collecting quality of life data that could be converted into
utility scores and resource data during in all future randomised controlled trials
would be useful, especially in pre-dialysis patients.

6.13.7 Recommendations

6.13.7.1 Once iron stores are replete (ferritin >150 µg/L and HRC <6% or TSAT> 20%),
people with anaemia of chronic kidney disease who are receiving ESAs, should be
given maintenance iron. The dosing regimen will depend on modality.
Haemodialysis patients will require the equivalent of 50-60mg intravenous iron per
week. In peritoneal dialysis and pre-dialysis patients intravenous iron requirements
should be dictated by iron indices.  \textbf{(D(GPP))}

\textit{See 3.2.2 for the associated algorithm}
6.14 ESAs: Monitoring Iron Status During Treatment

6.14.1 Clinical Introduction

6.14.1.1 Measurement of ferritin together with %HRC or %TSAT provides an indication of iron stores and availability of iron for erythropoiesis. We know that in patients with anaemia associated with CKD who are under treatment with ESAs an adequate supply of iron is essential for effective erythropoiesis and cost-efficient use of ESAs. We also know that too much iron may expose patients to risk of infectious complications and may also increase cardiovascular risk through oxidative stress. What then are the most desirable levels of these parameters of iron status to be maintained during treatment with ESAs?

6.14.2 Clinical Methodological Introduction

6.14.2.1 A literature search identified four studies consisting of a RCT 105, a cohort study 299, a prospective longitudinal study 300 and a prospective longitudinal study in children 301.

6.14.2.2 One study 302 did not meet quality criteria and was therefore excluded from the evidence statements.

6.14.2.3 Of note:

- In the study comparing TSAT 20-30% vs. 30-50% 105, achieved TSAT levels were 27.6% and 32.6% in the respective groups at the end of the 6-month study period

6.14.3 Clinical Evidence Statements

**Serum ferritin**

**Haemodialysis patients**

6.14.3.1 Intravenous iron supplementation which led to an increase in mean ferritin to 395 ± 206 mg/dl (P value not given) in children aged 10-17 years (N=8) lead to an increase in the Hb (P=0.0117) and Hct (P=0.0024), despite a fall in epoetin dose from 6,500 U to 6,150 U with no side effects noted, particularly hypertension 301.

Level 3

6.14.3.2 In a 24 month study (N=396) 303 Hb was maintained at a median level of 11.3 to 11.8 g/dl and median epoetin dose decreased to 72 (IQR 33-134) (P<0.001) when compared to baseline, when patients with serum ferritin <500 ng/ml were treated with concomitant IV iron sucrose regimen.

Level 3+
Transferrin saturation (TSAT)
Haemodialysis patients

6.14.3.3 In a study comparing the effects of TSAT 20-30% vs. 30-50% on epoetin dose required to maintain Hb 9.5-12.0 g/dl, epoetin dose progressively decreased in the TSAT 30-50% group, with ~40% dose reduction in months 4, 5 and 6 when compared to the 20-30% group ($X^2 = 15.50, P=0.0038$). This change in epoetin dose was independent of baseline dose in both the TSAT 30-50% group and TSAT 20-30% group.$^{105}$

Level 1+

Percentage of hypochromic red cells (%HRC)
Haemodialysis patients

6.14.3.4 In an 8-week study whereby patients stratified by baseline %HRC 0-3%, 4-9% and ≥10% received a fixed epoetin dose and IV iron saccharate 200 mg once weekly up to serum ferritin 250 µg/l, although mean Hb and ferritin levels significantly increased in all 3 groups ($P \leq 0.001$ for all), mean Hb increase was greater with increasing %HRC at baseline ($P=0.02$). In addition the proportion of patients with >1 g/dl increase in Hb was greater as %HRC at baseline increased ($P=0.02$)$^{299}$. 

Level 2+

6.14.4 Health Economic Methodological Introduction

6.14.4.1 Three studies were appraised$^{297, 105, 304}$ and two met quality criteria$^{105, 304}$. The study that did not meet quality criteria estimated cost-savings based on average reduced EPO dosages$^{297}$. However, with no inclusion of the prices used, the costing was not sufficiently transparent to warrant inclusion.

6.14.4.2 An American study estimated the cost-savings per patient per year over a 6-month period while maintaining TSAT between 30 and 50% vs. 20 to 30% using maintenance intravenous iron dextran$^{105}$.

6.14.4.3 One American study was a cost analysis of erythropoietin (EPO) using percent reduction of urea (PRU) as index of dialysis adequacy and transferrin saturation as a measure of iron stores. The study investigated two comparisons: the total dose of EPO received during the 4-week study by the 20 participants with the highest transferrin saturation to the 20 participants with the lowest transferrin saturation and the total dose of EPO administered during the 4-week study to the 20 patients with the highest PRU to the 20 participants with the lowest PRU$^{304}$. 

Anaemia in CKD: full guideline DRAFT (January 2006)  Page 163 of 229
6.14.5 Health Economic Evidence Statements

6.14.5.1 Study estimated intravenous iron dextran saves approximately $109 per month or $1308 per year per patient when maintaining the TSAT between 30 and 50% (n=23) (vs. 20 to 30% in control group; n=19) \(^{105}\). Cost difference between the intervention and control group was statistically significant by third month of study and remained significant until the end of the study at 6 months (p<0.02) \(^{105}\).

6.14.5.2 At $10 per 1,000 units of EPO, it costs $45 (10.2%) more per month per patient in the 20 patients with the lowest transferrin saturation compared to the 20 patients with the highest transferrin saturation \(^{304}\).

6.14.6 From Evidence to Recommendations

6.14.6.1 The GDG agreed that there was very little long-term effectiveness data to determine the most appropriate maintenance levels. The GDG based their recommendation on the European Best Practice Guidelines \(^{305}\).

6.14.7 Recommendations

6.14.7.1 In patients on maintenance therapy with ESAs, iron supplements should be given to keep:

- The serum ferritin between 200 and 500 μg/l in haemodialysis and between 100 and 500 μg/l in non-haemodialysis patients (D) and either
- The transferrin saturation level above 20% (unless ferritin >800 ug/L) (B)

or
- percentage hypochromic red cells (%HRC) less than 6% (unless ferritin >800ug/L) (D(GPP))
7 Monitoring of ACKD Treatment

7.1 Monitoring Iron Status

7.1.1 Clinical Introduction

7.1.1.1 Monitoring of iron status should be aimed at ensuring that patients undergoing treatment with ESAs maintain levels of iron that ensure maximally effective erythropoiesis. The frequency of monitoring must take account of the stage of anaemia treatment i.e. initial correction of anaemia or maintenance of target range of haemoglobin; the frequency and mode of iron supplementation; CKD status (HD patients have an obligatory loss of iron through the dialysis process); clinical situations likely to result in depletion of iron stores such as bleeding and surgery; clinical situations likely to result in misinterpretation of iron parameters e.g. co-existent infection leads to falsely elevated ferritin levels and depressed %TSAT; and pre-existing iron-overload states. The frequency of monitoring may also be dictated by the availability of the patient and by trend analysis of changes in iron status over time.

7.1.2 Methodological Introduction

7.1.2.1 A comprehensive literature search identified a cohort study 280.

7.1.2.2 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no health economic evidence statements are given.

7.1.3 Evidence Statements

Monitoring after intermittent iron dosing

_Haemodialysis patients_
Table 41: Time profile of intermittent IV iron dextran dosing regimen (N=14)

<table>
<thead>
<tr>
<th>Tx with 1,000 mg iron dextran over 10 doses</th>
<th>T=0</th>
<th>T=3 days</th>
<th>Time averaged value over 4 months after completion (trapezoid method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSAT (%)</td>
<td>20.6 ± 2.0 (range 15-37)</td>
<td>93 ± 6 (range 63-134)</td>
<td>30.1</td>
</tr>
<tr>
<td>T=0</td>
<td>T=2 months (peak value)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>197 ± 31 (range 27-424)</td>
<td>351</td>
<td></td>
</tr>
<tr>
<td>T=0</td>
<td>T=3 months</td>
<td>T=4 months</td>
<td></td>
</tr>
<tr>
<td>TIBC (µg/ml)</td>
<td>210 ± 7 (166-246)</td>
<td>180 ± 7</td>
<td>192 ± 11</td>
</tr>
</tbody>
</table>

**Level 2+**

Monitoring after single iron dose

*Haemodialysis patients*

Table 42: Time profile of single dose IV iron dextran 50 mg or 100 mg (N=16)

<table>
<thead>
<tr>
<th>T=0</th>
<th>Time averaged over 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSAT (%) Mean 34.6 ± 3.1 (N=16)</td>
<td>➢ 35.5 for 50 mg group (N=8) ➢ 36.7 for 100 mg group (N=8)</td>
</tr>
<tr>
<td>T=0</td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/ml) 231 ± 29 (N=16)</td>
<td>T=1 week, 297 ± 44 (N=16) T=2 weeks, 276 ± 35 (N=16)</td>
</tr>
<tr>
<td>T=0</td>
<td>Time averaged over 2 weeks</td>
</tr>
<tr>
<td>TIBC (µg/ml) Not reported</td>
<td>No change (data not reported)</td>
</tr>
</tbody>
</table>

**Level 2+**

7.1.4 From Evidence to Recommendations

7.1.4.1 The GDG agreed on a range of possible intervals for iron stores monitoring, which will allow practice to be tailored to the individual patient and to local systems. It is clear from the evidence that monitoring soon after intravenous iron is not helpful, and the GDG felt that a minimum time elapsed of 1 week would be appropriate.
7.1.5 Recommendations

7.1.5.1 People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. (C)

7.1.5.2 Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months. (D(GPP))

7.2 Monitoring Haemoglobin

7.2.1 Clinical Introduction

7.2.1.1 The initial step in clinical management of the CKD patient maintained in an anaemia programme must be the acquisition of laboratory and treatment data at specified intervals. The frequency of acquisition of data has been driven by anaemia treatment algorithms and decision matrices designed to achieve the required rate of rise of haemoglobin during the correction phase, and the desired haemoglobin level during the maintenance phase. However, the effectiveness of such algorithms and decision matrices is difficult to evaluate because there is a lack of published clinical outcomes related to their use. Furthermore, there is inherent variability in haemoglobin levels within a given population, and there are several components of this variability. One component is population or interpatient variability. Biological variability is found with nearly all laboratory measurements and in the case of haemoglobin levels in patients with CKD multiple factors contribute including gender and race, environmental factors, assay or sampling differences, the patient’s state of hydration and other related physiological determinants. Another component of haemoglobin level variability is individual or intraindividual variability. Here there is variation with repeated measurements over time in the same individual. Again there are multiple factors contributing to this variability including seasonal variations, sampling methods, co-morbid conditions such as nutritional status, inflammation, gastrointestinal bleeding, and bone marrow fibrosis. Two major factors are under control of the anaemia management team, ESA and iron therapy, and these are also determinants of haemoglobin level and factors in population variability. The physiological characteristics of erythropoiesis are such that there is a time required for the bone marrow to react to changing ESA stimulus and that reaction time varies widely among patients with CKD, ranging from a few weeks to a few months. It requires 1 to 2 months to induce red blood cell production and 1 to 3 after removal of ESA stimulus for patients to experience turnover of red blood cells to cease production. Data from a 1 year study demonstrates that haemoglobin levels may change from less than 11 g/dL to greater than 12 g/dL (or vice versa) in more than 28% of patients.306
Haemoglobin synthesis, red blood cell production and destruction are not processes that can be controlled instantaneously and haemoglobin level undershooting or overshooting should be expected when health professionals react to single haemoglobin values. We should therefore react to trends in haemoglobin levels but how frequently should the haemoglobin level be monitored to determine the trend?

7.2.2 Methodological Introduction

7.2.2.1 A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

7.2.3 From Evidence to Recommendations

7.2.3.1 Monitoring is part of care in ESA induction and maintenance, including consideration of the rate of haemoglobin change. The GDG felt that a range of intervals would allow monitoring to be tailored to the patient and the local systems, and agreed on 2-4 weeks in induction and 1-3 months in maintenance.

7.2.4 Recommendations

7.2.4.1 In people with anaemia of chronic kidney disease, haemoglobin should be monitored: (D(GPP))
- every 2-4 weeks in the induction phase of ESA treatment
- every 1-3 months in the maintenance phase of ESA treatment
- more actively after an ESA dose adjustment
- in a clinical setting chosen in discussion with the patient, taking into consideration their convenience and local health care systems

7.3 Detecting ESA Resistance

7.3.1 Clinical Introduction

7.3.1.1 The physiological characteristics of erythropoiesis are such that there is a time required for the bone marrow to react to ESA stimulus and that reaction time varies widely among patients with CKD, ranging from a few weeks to a few months. The magnitude of reaction to ESA stimulus is also variable. In determining resistance to
ESA therapy it is important to distinguish between true resistance, a lack of bone marrow response to ESA therapy, and apparent resistance where increased red cell destruction or red cell loss offsets ESA stimulated red cell production. It is also important to determine a dose threshold of ESA above which resistance to therapy is defined and a duration of therapy beyond which resistance to therapy should be suspected.

7.3.2 Methodological Introduction

7.3.2.1 A literature search identified a case series 307 and a cohort study 308.

7.3.2.2 Five studies 309,310,311,312,313 did not meet quality criteria and were therefore excluded from the evidence statements.

7.3.2.3 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.

7.3.3 Evidence Statements

**Pure red cell aplasia (PRCA)**

Haemodialysis patients

7.3.3.1 In a series of patients predominantly receiving epoetin alpha by the s.c. route, serum from all epoetin-treated patients (N=13) inhibited growth of erythroid cells and addition of epoetin to their serum samples reversed inhibitory effects. Also serum from all patients was shown to bind to epoetin and Scatchard analysis suggested presence of homogeneous binding sites 314.

Level 3

**Aluminium toxicity**

Haemodialysis patients

7.3.3.2 In a study conducted to maintain Hct 30% (Hb ~10 g/dl), where patients were divided into 2 groups on the basis of response to epoetin treatment, the poor responders received a higher epoetin dose (P<0.05), yet had lower Hb and Hct levels (both P<0.001). Of the haematological parameters investigated, basal aluminium and aluminium levels following challenge with desferrioxamine were higher in the poor responders (both P<0.01). In addition, mean corpuscular volume showed inverse correlation with basal aluminium (data not provided), post-desferrioxamine aluminium (r=-0.617, P=0.005) and change in aluminium levels (r=-0.711, P<0.001) in the poor responders. In the good responders, mean corpuscular volume only showed correlation with change in aluminium levels (r=-0.476, P=0.03) 308.

Level 2+
7.3.4 From Evidence to Recommendations

7.3.4.1 When considering when resistance to ESAs should be suspected and what conditions lead to ESA resistance the GDG reviewed evidence on two outcomes, PRCA and aluminium toxicity.

7.3.4.2 The GDG considered the definition of resistance and agreed on the definition suggested by the Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure. It was agreed to suspect resistance when a patient does not achieve the target Hb level after receiving an epoetin dose more than 300 units/kg/week s.c. (approximately 20,000 units/week) or equivalent or 1.5 μg/kg darbepoetin alfa s.c. or i.v. (approximately 100 μg/week) or has a continued need for the administration of high doses of ESAs to maintain the target Hb level315. It was noted that 300 units/kg/week is used as this value is 2 standard deviations of the mean value used. The GDG considered that resistance should be suspected after 3 months of failure to respond to ESAs, after exclusion of other causes of a temporary lack of response (e.g. intercurrent illness or other causes of chronic bleeding).

7.3.4.3 With regards to conditions that lead to ESA resistance the GDG reviewed evidence on PRCA. The GDG agreed their working definition of PRCA to be the presence of a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered PRCA to be confirmed where anti-erythropoietin antibodies are present (as shown by an appropriate laboratory assay) and there was a lack of pro-erythroid progenitor cells in the bone marrow. The GDG noted that PRCA can be induced by other causes aside from sensitisation to Epoetin. This has since been addressed by using a fluoro-resin coating, which forms a barrier between the rubber stopper and epoetin in some pre-filled syringes. The evidence presented specifically addressed PRCA induced by sensitisation to epoetin and demonstrated that the inhibition of the erythroid cells was correlated with the presence of anti-epoetin antibodies316.
7.3.4.4 The GDG noted that the issue of aluminium toxicity was of clinical importance but the incidence is now very rare. Although, the GDG noted that there was a current source of aluminium from the responsible use of aluminium hydroxide capsules (Alu-caps; used as phosphate binders to reduce the absorption of dietary phosphate). It was considered unlikely that the use of Alu-caps would lead to aluminium toxicity. The issue of toxicity originally stemmed from a lack of water purity which has improved. It was noted that the trial 308 did not report either the use of aluminium-based phosphate binders or whether any water purification system was being used. The GDG noted that it was noted that aluminium levels are routinely measured in their haemodialysis patients but that the need to continue doing so was under question.

7.3.5 Recommendations

7.3.5.1 After other causes such as intercurrent illness or chronic blood loss have been excluded, patients with CKD should be considered resistant to ESAs when a patient: (D(GPP))

- does not achieve the target Hb level despite:
  - receiving a epoetin dose more than 300 units/kg/week (approximately 20,000 units/week) or
  - receiving 1.5 µg/kg darbepoetin alfa (approximately 100 mg/week) or
  - receiving an equivalent dose of other ESAs or
- has a continued need for the administration of high doses of ESAs to maintain the target Hb level.

7.3.5.2 In patients with CKD, pure red cell aplasia (PRCA) should be confirmed by the presence of a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered PRCA to be confirmed where anti-erythropoietin antibodies are present and there was a lack of pro-erythroid progenitor cells in the bone marrow. (D)

7.3.5.3 In patients 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. (C)

See 3.2.5 for the associated algorithm.

7.4 Managing ESA Resistance

7.4.1 Clinical Introduction

7.4.1.1 Management of ESA resistance will clearly depend on the underlying cause. The Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD-2) identified
an incidence of inadequate ESA response of 16.7 per 1000 patients years on ESA while on dialysis. Fifty-seven of 1677 patients with incident end stage renal disease in the NECOSAD-2 study had an inadequate ESA response, table X below shows the various causes identified.

Table 43. Possible causes for ESA resistance from the NECOSAD-2 study (N = 57)

<table>
<thead>
<tr>
<th>Causes for inadequate ESA Response</th>
<th>Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/inflammation</td>
<td>41</td>
</tr>
<tr>
<td>Blood loss</td>
<td>16</td>
</tr>
<tr>
<td>Hyperparathyroidism/aluminum toxicity</td>
<td>10</td>
</tr>
<tr>
<td>Haemoglobinopathy</td>
<td>2</td>
</tr>
<tr>
<td>Folate/vitamin B12 deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma/myelofibrosis/myelodysplastic syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>5</td>
</tr>
<tr>
<td>Inadequate dialysis</td>
<td>2</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>0</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
</tr>
<tr>
<td>Graft/shunt problems</td>
<td>14</td>
</tr>
<tr>
<td>Operation</td>
<td>8</td>
</tr>
<tr>
<td>Suspected noncompliance</td>
<td>9</td>
</tr>
<tr>
<td>Medication (≥bone marrow suppress)</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

*Some patients fell into more than one category (i.e. there was more than one possible cause for their inadequate ESA response).

7.4.2 Methodological Introduction

7.4.2.1 The literature search identified three studies which consisted of a 2-part study, with a prospective cohort group and a subsequent before and after study in a sub-group, a retrospective case series and a before and after study.

7.4.2.2 A comprehensive literature search did not identify any studies that were suitable to address the economic aspects of this section, therefore no evidence statements are given.
7.4.3 Evidence Statements

Treatment of aluminium toxicity with desferrioxamine

Dialysis patients

7.4.3.1 Patients receiving epoetin with no concurrent or prior treatment for aluminium toxicity (N=5) had a low mean rise of Hb above baseline and did not achieve target Hb 9 g/dl over 20 weeks, unlike the control groups with treatment prior to the study (N=4) (P<0.05) and no aluminium toxicity (N=8) (P<0.05), which reached target Hb within 12 weeks of the study. This was supported by the correlation between baseline serum aluminium levels and the mean rise of Hb (r=-0.51, P=0.03) and between Hb rise during epoetin therapy and aluminium increment following challenge with desferrioxamine.

Level 2+

7.4.3.2 In addition, concurrent treatment with desferrioxamine in this group led to a mean Hb rise when compared to previous treatment with epoetin only (P<0.01).

Level 3

Reduced T-cell production of inflammatory markers TNF-alpha and IFN-gamma with low dose pentoxifylline

AMCKD patient population not specified

7.4.3.3 Hb levels in poor responders to epoetin (N=12) significantly improved after 4 months treatment with low dose pentoxifylline (P=0.0001). This was associated with a decrease in TNF-alpha (P=0.0007) and IFN-gamma (P=0.0002) production 6-8 weeks following pentoxifylline therapy, and no change in white blood cell production after 4 months. This suggestive evidence was supported by a correlation between change in Hb and TNF-alpha production (r_s=0.7145; P=0.0118), however, no correlation was found between change in Hb and IFN-gamma (r_s=0.4406; P=0.1542).

Level 3

Treatment of ESA-induced pure red cell aplasia (PRCA) with immunosuppressants / immunoglobulins/ kidney transplant

Not on dialysis, haemodialysis and peritoneal dialysis patients

7.4.3.4 In a group of patients with epoetin-induced PRCA (N=43 epoetin alpha ± epoetin beta or darboepoetin and N=4 epoetin beta exclusively), 37 patients received treatment which consisted of 1 treatment (N=26), 2 consecutive treatment regimens (N=10) or 5 different regimens (N=1). Of these, 29 patients recovered (i.e. reticulocyte counts >20,000/µl and not requiring red cell transfusions), however, no patient was challenged with ESA. As the treatments are not comparable for superiority, the data from the study is presented here.
### Table 44: PRCA Treatment

<table>
<thead>
<tr>
<th>PRCA Treatment</th>
<th>N</th>
<th>No. of patients who recovered</th>
<th>Time before recovery (months)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids alone (N=14) ± high dose i.v. immunoglobulins</td>
<td>18</td>
<td>10 (56%)</td>
<td>1†, 2†, 2†, 3†, 3†, 3†, 3†, 3†, 6†, 18†</td>
<td>3, 3, 3, 3, 5†, 13†, 20, 30†</td>
</tr>
<tr>
<td>High dose i.v. immunoglobulins alone</td>
<td>9</td>
<td>1 (11%)</td>
<td>3†</td>
<td>3, 3, 4, 4, 4, 9, 10†, 19</td>
</tr>
<tr>
<td>Corticosteroids + cyclophosphamide</td>
<td>8</td>
<td>7 (87%)</td>
<td>1†, 2, 2, 3†, 4, 5, 7</td>
<td>3</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>6</td>
<td>4 (67%)</td>
<td>1†, 1†, 1†, 1†</td>
<td>3, 9†</td>
</tr>
<tr>
<td>Kidney transplant*</td>
<td>6</td>
<td>6 (100%)</td>
<td>&lt;1†, &lt;1†, &lt;1†, &lt;1†, &lt;1†, &lt;1, &lt;1†</td>
<td>-</td>
</tr>
<tr>
<td>Antibodies to CD20</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>3†, 3</td>
</tr>
<tr>
<td>Corticosteroids + high dose i.v. immunoglobulins + plasma exchange</td>
<td>1</td>
<td>1 (100%)</td>
<td>3†</td>
<td>-</td>
</tr>
<tr>
<td>Mycophenolate motefil</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>12</td>
</tr>
</tbody>
</table>

N.B. For patients who didn’t recover, follow-up was length of time between start of Tx and last visit or start of new Tx

†Received only 1 kind of Tx

* Received induction Tx followed by triple immunosuppressive therapy

**Level 3**
7.4.4 From Evidence to Recommendations

7.4.4.1 When considering how ESA resistance should be managed the GDG reviewed evidence on three outcomes, aluminium toxicity, markers of inflammation and the treatment of PRCA.

7.4.4.2 The GDG noted that with regards to treating aluminium toxicity that desferrioxamine was considered the treatment of choice. If aluminium toxicity was suspected, a patient should be administered a bolus of desferrioxamine and the amount of aluminium flushed into the blood stream determined. Treatment with desferrioxamine should be administered until aluminium toxicity is no longer present. The GDG noted that it was rare to find patients with toxic levels of aluminium and that this should be considered a special circumstance that would be most likely to occur in haemodialysis patients managed by renal physicians.

7.4.4.3 With regards to inflammatory markers, the GDG reviewed one study that suggested that in poor responders to ESAs, treatment with low-dose pentoxifylline reduced the production of inflammatory markers (TNF-alpha and IFN-gamma) by T-cells \(^{320}\). However, the GDG cautioned that this was an academic scientific study that, although interesting, did not reflect current clinical practice and noted that pentoxifylline was not licensed for this use. The GDG felt that clinical trials were needed to support this data.

7.4.4.4 The GDG reviewed evidence on the treatment of ESA-mediated PRCA. The GDG felt this was a specialised area with few annual cases. Due to this, the GDG acknowledged that the treatment of this condition was not fully established and that the most up-to-date information was available on-line and was written by the PRCA Global Scientific Advisory Board (GSAB; [http://www.prcaforum.com/treatment.php] \(^{322}\) and this should be accessed to determine the current best practice to treat this condition. The GDG noted that immunosuppressive therapies have been shown to reverse antibody-mediated PRCA. However, it was noted that the total number of patients with this condition was so small that they felt unable to recommend this treatment. The GDG noted that GSAB suggested that cyclosporine was currently suggested as the treatment of choice.

7.4.5 Recommendations

7.4.5.1 In haemodialysis patients with anaemia of CKD where aluminium toxicity is suspected a desferrioxamine test should be performed and the patient managed accordingly. (C)
7.4.5.2 In patients with anaemia of CKD, ESA-induced PRCA should be managed in accordance with current best practice. Specialist referral should be considered. N.B. Current best practice for this rare condition is available on-line from the PRCA Global Scientific Advisory Board (GSAB; http://www.prcaforum.com/treatment.php).

See 3.2.5 for the associated algorithm.
8 Research Recommendations

- A prospective study of adequate duration of IV iron preparations in children with ACKD, including safety, dosing and efficacy outcomes.

- Trials of ESAs in children with ACKD (including darbepoetin which is currently unlicensed in children under 12), including safety, dosing and efficacy outcomes.

- Optimal Hb levels to be achieved with ESAs in children with ACKD

- Observational study of Hb levels and adverse outcomes in older people

- The usefulness of an EPO tolerance test to determine which patients will respond well to ESAs and if those patients found to respond well could be treated to lower optimal Hb levels than those who do not.

- Are the same levels of serum ferritin, %HRC and %TSAT that define functional iron deficiency in dialysis patients applicable to the pre-dialysis population?

- The diagnostic value of endogenous erythropoietin testing

- A RCT study to assess Hb level as an outcome in pre-dialysis patients treated to a serum ferritin levels < 200μg/l versus those treated to 300 – 500 μg/l.

- Which patients would most benefit from ESA treatment in the wider CKD population?

- Does the co-administration of ESAs with physiological doses of androgens reduce the dose of ESA administered?
## Appendix A: Evidence-based clinical questions and literature searches

Table 45:

<table>
<thead>
<tr>
<th>Question ID</th>
<th>Question wording</th>
<th>Study Type Filters used</th>
<th>Databases and Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROG1</td>
<td>In patients with chronic kidney disease, what haemoglobin (Hb) / haematocrit levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?</td>
<td>All study types</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>DIAG1</td>
<td>In patients with chronic kidney disease, what is the association between glomerular filtration rate (GFR) and haemoglobin levels in a) diabetic and b) non-diabetic patients?</td>
<td>All study types</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>MGTFE1</td>
<td>Up to what levels of serum ferritin, percentage transferrin saturation (%TSAT) and percentage hypochromic red cells (%HRC) should patients with ACKD be treated with iron without adverse events?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGTFE2</td>
<td>In patients with ACKD what, if any, are the serum ferritin, transferrin saturation (%TSAT) and percentage hypochromic red cells (%HRC) thresholds for commencing treatment with ESAs</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>MGTFE3</td>
<td>In patients with ACKD what, if any, are the optimal serum ferritin, transferrin saturation and percentage hypochromic red cells (%HRC) levels to be maintained during treatment with ESAs?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>TXEF1</td>
<td>In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin alfa compared to epoetin beta in reducing morbidity and mortality and improving quality of life?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>TXEF2</td>
<td>In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin alfa compared to darbepoetin in reducing morbidity and mortality and improving quality of life?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>TXEF3</td>
<td>In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin beta compared to darbepoetin in reducing morbidity and mortality and improving quality of life?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>TXEF4</td>
<td>In patients with ACKD what are the benefits and risks of correcting anaemia with ESAs compared to placebo or no treatment in reducing morbidity and mortality and improving quality of life?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>TXDF2</td>
<td>In patients with ACKD, what factors determine the dose and frequency of ESA required to keep the haemoglobin level within the maintenance range?</td>
<td>Systematic reviews and RCTs and comparative studies</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>MON1</td>
<td>In patients with ACKD treated with ESAs, how frequently should iron status be checked?</td>
<td>All study types</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
<tr>
<td>MON2</td>
<td>In patients with ACKD treated with ESAs, how frequently should haemoglobin levels be checked a) during Hb correction and b) during Hb maintenance</td>
<td>All study types</td>
<td>Medline 1966 –2005 Embase 1980-2005 Cochrane 1800-2005 Cinahl 1982-2005</td>
</tr>
</tbody>
</table>

NOTE: The final cut-off date for all searches was 28 September 2005.
Appendix B: Scope

National Institute for Clinical Excellence

Guideline title
Anaemia management in people with chronic kidney disease (CKD)

Short title
Anaemia in chronic kidney disease

Background
a) The National Institute for Clinical Excellence (‘NICE’ or ‘the Institute’) has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on the management of anaemia in chronic kidney disease (CKD) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see Appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute’s clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework. The NSF for Renal Services (2004) is of particular relevance to this guideline.

Clinical need for the guideline
a) The NSF for Renal Services (2004) defines chronic kidney disease (CKD) as kidney (renal) disease that is irreversible and progressive. Established renal failure (also called end stage renal failure) is CKD that has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) is needed to maintain life.
b) Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only. Conventionally the total number of people receiving renal replacement therapy has been taken as a proxy measure for the prevalence of established renal failure. The NSF for Renal Services estimates that more than 27,000 people received renal replacement therapy in England in 2001. Approximately one-half of these had a functioning transplant and the remainder were on dialysis. It is predicted that numbers will rise to around 45,000 over the next ten years. However, the most recent Renal Registry Report (2003) states that 32,500 patients received renal replacement therapy with 46% having a renal transplant.

c) The UK Renal Registry Report (2003) highlights that 43% of patients newly receiving dialysis had a haemoglobin level of <10g/dl in 2002. This is despite the fact that patients receiving dialysis treatment during 2002 had haemoglobin concentrations that continued to improve. The Registry demonstrated that 82% of haemodialysis patients and 88% of peritoneal dialysis patients had a haemoglobin concentration >10g/dl.

d) The clinical need for the guideline is supported by the wide variation in practice and lack of agreement on the optimal management of renal anaemia. The UK Renal Registry Report (2003) draws attention to the fact that it was not possible to provide accurate information about erythropoietin because of variations in the recording of erythropoietin data and also the provision of erythropoietin from primary care in some parts of the UK. An evidence-based guideline should improve the standards of care across renal units and aid appropriate commissioning of cost-effective treatments.

**The guideline**

a) The guideline development process is described in detail in two publications which are available from the NICE website (see ‘Further information’). *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS* describes how organisations can become involved in the development of a guideline. The *Guideline*
Development Methods – Information for National Collaborating Centres and Guideline Developers provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see Appendix).

c) The areas that will be addressed by the guideline are described in the following sections.
**Population**

**Groups that will be covered**

a) The guideline will offer best practice advice on the care of people who have a clinical diagnosis of anaemia associated with CKD.

b) The guideline will encompass the care of people with pre-dialysis CKD, people with established renal failure receiving renal replacement therapy, people with established renal failure receiving conservative management, and people after renal transplant surgery.

c) The guideline will cover children (aged <16 years).

**Groups that will not be covered**

a) Where CKD is not the principal cause of the anaemia it will be excluded, for example:

- Anaemia caused by haematological disease.
- Anaemia caused by acute and chronic inflammatory disease states.
- Anaemia caused by malignancy.
- Anaemia caused by acquired immunodeficiency syndrome.
- Anaemia caused by acute renal failure.

**Healthcare setting**

The guideline will cover the care provided by healthcare professionals in direct contact with patients with anaemia associated with CKD and make decisions about their care. This will include healthcare professionals in primary, secondary and tertiary NHS care settings.

**Clinical management**

The guideline will include recommendations in the following areas.

a) Detection and diagnosis of anaemia in people with CKD:

- Exclusion of other causes of anaemia.
• Diagnostic evaluation of anaemia in CKD.

• Assessment of anaemia.

b) Criteria for the threshold levels of haemoglobin concentration for initiating the treatment of anaemia.

c) factors which have an impact on anaemia in renal disease and their management including:

• Nutritional status including haematinics.

• Dialysis adequacy (peritoneal and haemodialysis).

• Hyperparathyroidism.

• Assessment and optimisation of erythropoiesis to include iron stores, iron supplements and erythropoiesis stimulating agents.

• Monitoring of treatment of anaemia associated with people with CKD.

Guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the Summary of Product Characteristics to inform their decisions for individual patients.

Status
Scope
This is the final version of the scope.

Guideline
The development of the guideline recommendations will begin in October 2004.

Further information
Information on the guideline development process is provided in:

• The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS

• Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers

These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.
Appendix – Referral from the Department of Health and Welsh Assembly Government
The Department of Health and Welsh Assembly Government asked the Institute:

“To develop a guideline for the NHS in England and Wales for the management of anaemia in people with poor renal function, including chronic kidney disease and established renal failure, based on evidence of clinical and cost effectiveness of interventions available for treating anaemia in such people. The interventions should be all those factors that have an impact on anaemia including nutritional status, dialysis effectiveness, iron stores and the use of recombinant human erythropoietin. The purpose of the guideline will be to take renal staff and patients through the most cost effective set of investigations and procedures which will optimise haemoglobin and if possible keep it above the accepted international standard, for example European and K-DOQI of 11 g/dl.”
Appendix C: Health Economic Model: Target haemoglobin in haemodialysis patients

Background
The treatment of anaemia in CKD helps increase the health-related quality of life of patients. However, the optimal haemoglobin target continues to be debated. While there is an economic evaluation on the cost-effectiveness of different targets based on US data, the lack of cost-effectiveness data in the UK warranted further investigation.

Aim
The aim of the model is to compare three alternative haemoglobin (Hb) targets in the anaemia management of haemodialysis patients over a 2-year period. The haemoglobin targets evaluated were: <11 g/dL, 11-12 g/dL and >12 g/dL. The cost per quality-adjusted life year gained was calculated.

Methods
A cost-effectiveness model was constructed from the perspective of the NHS. The effectiveness outcome measure used was quality-adjusted life years (QALYs) and the incremental cost per QALY was calculated. Point estimates are derived from probabilistic results.

Incremental cost per QALY = (C1 – C2) / (Q1 – Q2)

Where:
C1 = Estimated cost of anaemia treatment to reach Hb target
C2 = Estimated cost of anaemia treatment to reach higher Hb target
Q1 = Estimated quality-adjusted life years from Hb target
Q2 = Estimated quality-adjusted life years from higher Hb target

The data sources of the costs and benefits are described in further detail in Tables 1-5. All costs and benefits were discounted at an annual rate of 3.5% in accordance with current NICE recommendations in their Guideline Development Methods 2005. Costs and benefits were accrued monthly over the two-year period. A one-month cycle was chosen as blood tests are routinely taken monthly in haemodialysis patients. A two-year time horizon was chosen as it was considered a clinically relevant time period of treatment considering transplantation rates and survival on dialysis. The 11-12 g/dL haemoglobin target was selected based on the GDG’s interpretation of the clinical data. This alternative was compared to below 11 g/dL and above 12 g/dL to assess the cost-effectiveness of these alternative strategies. All costs are in pound sterling with base-year 2005. One-way sensitivity analysis and a cost-effectiveness acceptability curve were constructed to assess the impact of uncertainty on the incremental cost-effectiveness ratio (ICER). Threshold analyses were performed to investigate the value of the utility of Hb target 11-12 g/dL for which the ICER becomes £30,000.
Data Sources and Assumptions

Tables 46-49 list the baseline cost and effectiveness outcomes along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Table 46. Dose of ESA for each Hb Target Range

<table>
<thead>
<tr>
<th>Model Target Hb (g/dL)</th>
<th>Hb Target in Source Study (g/dL)</th>
<th>Type of ESA</th>
<th>IU/wk</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>10 ± 1</td>
<td>Epoetin-alfa</td>
<td>10,671 (SD 7,236, n=18)</td>
<td>323</td>
</tr>
<tr>
<td>11-12</td>
<td>&gt;11.0</td>
<td>Epoetin-alfa/beta Sc&amp;iv</td>
<td>10,831 (n=189)*</td>
<td>324</td>
</tr>
<tr>
<td>&gt;12</td>
<td>13.5-16.0</td>
<td>Epoetin-alfa Sc</td>
<td>236 (U/kg/wk) (SD 148, n=157)</td>
<td>325</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15,340** (SD 148.3, n=157) (Estimate)</td>
<td></td>
</tr>
</tbody>
</table>

*No standard deviation given in study. Assumed same %SD of IU/wk as <11. (67.8%, estimated SD 7,344)

**assuming 65 ± 10 kg average weight

Mean epoetin values in table 1. were derived from RCT data where possible and selected based on the target haemoglobins in the studies being the closest to <11, 11-12 and >12 g/dL.

The cost of epoetin was calculated using a unit cost of £7.96 for 1,000 units of epoetin alfa and pre-filled syringe from the British National Formulary (BNF) 49.

Table 47. Calculations per Month

<table>
<thead>
<tr>
<th>IU/month of ESA</th>
<th>Cost per month (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,398.80</td>
<td>369.33</td>
</tr>
<tr>
<td>47,094.50</td>
<td>374.87</td>
</tr>
<tr>
<td>66,700.18</td>
<td>530.93</td>
</tr>
</tbody>
</table>
### Table 48. All-Cause Mortality

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>Deaths/1000 treatment-yr (Adjusted)*</th>
<th>RR (Adjusted) Per month cycle: (mortality rate, standard error)</th>
<th>Deaths/1000 treatment-yr (Unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11</td>
<td>249</td>
<td>1.25 (.021, .0045)</td>
<td>259</td>
</tr>
<tr>
<td>11-12</td>
<td>199</td>
<td>1 (.016, .0040)</td>
<td>199</td>
</tr>
<tr>
<td>&gt;12</td>
<td>197</td>
<td>0.99 (.016, .0040)</td>
<td>192</td>
</tr>
</tbody>
</table>

Source: 45
*Calculated using unadjusted rate and RR

### Table 49. Utility

<table>
<thead>
<tr>
<th>Model Target Hb (g/dL)</th>
<th>Hb Target in Source Study (g/dL)</th>
<th>Value</th>
<th>Measurement Technique</th>
<th>N</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11</td>
<td>9.5-11.0 (10.2 ± 1.0)</td>
<td>0.51</td>
<td>Time-Trade Off</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>11-12</td>
<td>-</td>
<td>0.545</td>
<td>-</td>
<td></td>
<td>(Estimate)*</td>
</tr>
<tr>
<td>&gt;12</td>
<td>11.5-13.0 (11.7 ± 1.4)</td>
<td>0.58</td>
<td>Time-Trade Off</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated the utility score of the Hb target 11-12 g/dL as the midpoint between the values for target Hb<11 and Hb>12. (.545)
No standard deviation given in study. Standard error of .02 (~10%SD) for each utility value.

### Explanation of assumptions and data used

#### Costs

Only costs specific to anaemia treatment rather than haemodialysis care and those that are different between the treatment strategies were included.

**Hb target <11 g/dL**
The monthly cost of reaching the Hb target was derived from the mean dose of ESA per week used in a randomised open-label trial comparing target Hb of 10 ± 1 g/dL and 14 ± 1 g/dL in 35 dialysis patients 328 and the unit cost of epoetin alfa in a pre-filled syringe. The total cost of care per patient was considered stable for the 2-year period.

**Hb target 11-12 g/dL**
The monthly cost of Hb target 11-12 g/dL was derived from the mean epoetin dose from the Results of the European Survey on Anaemia Management in 2003 (ESAM) 324 based on 189 haemodialysis, haemofiltration and haemofiltration patients in the UK and the unit cost of epoetin alfa in a pre-filled syringe.
Hb target >12 g/dL
The monthly cost of Hb target >12 g/dL was derived from the mean units/kg/week of epoetin from a randomised controlled trial of 157 haemodialysis patients treated to a target Hb range of 13.5-16.0 g/dL and the unit cost of epoetin alfa in a pre-filled syringe. It was assumed an average patient would be 65 ± 10 kg in order to calculate the mean units/week.

Other cost drivers that were assumed to be the same regardless of the Hb target range were:
- consultation time and type of health professional responsible for anaemia management
- iron strategy
- haemodialysis treatment (considered part of standard care)

QALYs

Hb target <11 g/dL, Hb target >12 g/dL
The quality of life in Hb target <11 g/dL and Hb target >12 g/dL were derived from a randomised study comparing placebo, 9.5-11.0 g/dL and 11.5-13.0 g/dL achieved Hb ranges in 118 haemodialysis. The results from the time trade off technique were used as the QALY weight in the estimation of QALYs. Although these were achieved Hb ranges, it was assumed that a target of >12 g/dL or <11 g/dL would have achieved haemoglobin levels similar to these ranges. Total QALY gain in each month cycle was added with a 3.5% annual discount rate.

Hb target 11-12 g/dL
The quality of life in target Hb 11-12 g/dL was estimated as the midpoint between the values for target Hb<11 and Hb>12. (545) This method of estimation was chosen on the following reasoning from the clinical evidence:
In quality of life studies > 6 months in duration there is statistically significant quality of life improvement in certain dimensions such as physical functioning.
There is significant improvement between 9.0-12.0 and 13.5-16.0 g/dL 325, 10 and 14 g/dL 329 and 10.2 and 12.5 g/dL  [Moreno, 2000 76 /id]. There is improvement (but not significant) between 9.5-11.0 and 11.5-13.0  [214 /id]. This suggests that the quality of life between 11-12 is probably not the same as >12, and probably is slightly less than it is in Hb >12 and more than <11, suggesting a linear estimation is reasonable.

Additional Assumptions

- There is no increased risk of access failure or hypertension with higher haemoglobin targets
- Concordance
- Rate of transplantation is equivalent in each treatment strategy
- Dialysis adequacy is equivalent in each treatment strategy
- Mean epoetin doses remain representative of costs over a 2-year period
• There is no difference in hospitalisation rates with different haemoglobin targets.

Observational studies suggest a difference in the number of hospitalisations and reduction in duration of stays \(^{45,48}\), however, it is very possible these values were not adjusted sufficiently for confounders. Two RCTs \(^{325,330}\) and the meta-analysis \(^{226}\) indicate there is no significant difference in rate and days of hospitalisation. Therefore, the rate of hospitalisation was not used in the model to differentiate between Hb targets.

**Mortality Rates**

The mortality rates used in the model were derived from the adjusted relative risk of death and all-cause mortality rates in patients in an observational study of 66,761 patients \(^{45}\). The GDG felt the evidence on mortality in the meta-analysis \(^{226}\) may be more biased by the weight given to one study on patients with cardiovascular disease \(^{331}\) than the observational study.

**Results**

**Table 50:** Probabilistic Model Results: 2-Year Time Horizon

<table>
<thead>
<tr>
<th>Hb Range (g/dL)</th>
<th>Cost (£)</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>7,202</td>
<td>0.79</td>
</tr>
<tr>
<td>11-12</td>
<td>7,750</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt;12</td>
<td>10,993</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**Table 51:** Probabilistic Incremental Results of Base-line Values

<table>
<thead>
<tr>
<th>Hb Range (g/dL)</th>
<th>Incremental Cost (£)</th>
<th>Incremental QALYs</th>
<th>ICER (£ per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-12 vs &lt;11</td>
<td>548</td>
<td>0.11</td>
<td>4,985</td>
</tr>
<tr>
<td>&gt;12 vs 11-12</td>
<td>3,242</td>
<td>0.07</td>
<td>47,458</td>
</tr>
</tbody>
</table>

Differences due to rounding

**Sensitivity Analysis**

The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The variables included reflect the mortality rates, costs, utilities and hospitalisation rates used in the deterministic model. Results for the upper and lower estimates are given in Table 52 and 53.
Table 52: One-way Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line Value</th>
<th>Range Evaluated</th>
<th>Hb Comparison</th>
<th>ICER Range Estimate (Dominant strategy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR death Hb &lt;11</td>
<td>1.25</td>
<td>1.20 - 1.30</td>
<td>11-12 vs &lt;11</td>
<td>4,369 - 4,999</td>
</tr>
<tr>
<td>RR death Hb &gt;12</td>
<td>0.99</td>
<td>0.92 - 1.07</td>
<td>&gt;12 vs 11-12</td>
<td>46,906 - 69,224</td>
</tr>
<tr>
<td>Cost per month cycle Hb &lt;11</td>
<td>369.33</td>
<td>118.89 - 619.78</td>
<td>11-12 vs &lt;11</td>
<td>55,808 Hb11-12</td>
</tr>
<tr>
<td>Cost per month cycle Hb 11-12</td>
<td>374.87</td>
<td>120.67 - 629.07</td>
<td>11-12 vs &lt;11</td>
<td>59,007 Hb11-12</td>
</tr>
<tr>
<td>Cost per month cycle Hb &gt;12</td>
<td>530.93</td>
<td>525.80 - 536.07</td>
<td>&gt;12 vs 11-12</td>
<td>53,026 - 56,617</td>
</tr>
<tr>
<td>Utility Hb &lt;11</td>
<td>0.51</td>
<td>0.46 - 0.56</td>
<td>11-12 vs &lt;11</td>
<td>2,589 - 26,632</td>
</tr>
<tr>
<td>Utility Hb 11-12</td>
<td>0.55</td>
<td>0.49 - 0.60</td>
<td>11-12 vs &lt;11</td>
<td>61,140 - 2,454</td>
</tr>
<tr>
<td>Utility Hb &gt;12</td>
<td>0.58</td>
<td>0.52 - 0.64</td>
<td>&gt;12 vs 11-12</td>
<td>21,018 Hb 11-12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line Estimates (No difference)</th>
<th>Observational Study Estimates</th>
<th>Cost of hospitalisation (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR of hospitalisation Hb &lt;11</td>
<td>1.0</td>
<td>1.21</td>
<td>2,190</td>
</tr>
<tr>
<td>RR of hospitalisation Hb 11-12</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>RR of hospitalisation Hb &gt;12</td>
<td>1.0</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>ICER Hb11-12 vs Hb&lt;11</td>
<td>4,719</td>
<td>1,444</td>
<td></td>
</tr>
<tr>
<td>ICER Hb&gt;12 vs Hb11-12</td>
<td>54,822</td>
<td>41,481</td>
<td></td>
</tr>
<tr>
<td>ICER Hb11-12 vs Hb&lt;11</td>
<td>3,719</td>
<td>863 (Lower Estimate)</td>
<td></td>
</tr>
<tr>
<td>ICER Hb&gt;12 vs Hb11-12</td>
<td>46,750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>ICER</td>
<td>Upper Estimate</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Hb&lt;11 vs Hb11-12</td>
<td>84</td>
<td>2,983</td>
<td></td>
</tr>
<tr>
<td>Hb&gt;12 vs Hb11-12</td>
<td>38,333</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The extent of uncertainty in the probabilistic model is displayed in Figure 5. Figure 6 summarises the uncertainty into probabilities that an alternative is cost-effective for a range of willingness to pay thresholds.
Discussion

Point estimates suggest Hb target 11-12 g/dL is the optimal strategy with a £20,000-30,000 threshold. Uncertainty was assessed in the deterministic results in a one-way and two-way sensitivity analyses (Tables 52-53). At the upper estimate of the monthly cost of Hb11-12 (£629.07), target Hb11-12 is dominated by Hb >12, the total costs in Hb11-12 are higher than Hb >12 but results in less QALYs. While the upper estimate is a plausible estimate of Hb11-12, it would mean the unlikely situation, in the absence of hospitalisation costs saved, where the monthly cost to reach Hb >12 is less than the monthly cost to reach Hb 11-12 (£530.93).

At the lower estimate of Hb 11-12 utility, the Hb11-12 vs Hb<11 ICER increased to £61,140 and the Hb>12 vs Hb11-12 ICER increased to £21,856. The lower estimate of Hb 11-12 (0.49) is less than the base-line estimate of Hb <11 (0.51), contrary to clinical evidence. Rather than to make an assumption about the utility of Hb target 11-12 g/dL per month, if we allow the utility to vary, the value at which the ICER of 11-12 g/dL vs. <11 g/dL target is £30,000 is 0.50. This would mean the utility of target Hb 11-12 g/dL not to be cost effective as defined by an ICER of £30,000 or less.

At the higher estimate of Hb 11-12 utility, Hb11-12 vs Hb<11 ICER decreased to £2,454 and the Hb 11-12 dominates (in this case Hb 11-12 costs less with more QALYs gained) Hb>12. This is reasonable as with the same costs and more QALYs gained in Hb11-12 will result in more favourable ICERs.

At the lower estimate of the utility of Hb>12, the Hb 11-12 strategy dominates Hb>12 (in this case Hb12 costs more with less QALYs gained) however, at the upper estimate, the Hb>12 vs Hb11-12 ICER decreased to £21,018.

Similarly, if we allow the utility of target Hb 11-12 g/dL to vary, the value at which the ICER of >12 g/dL vs. 11-12 g/dL is £30,000 is 0.52. This would mean the utility of target
Hb 11-12 g/dL would be much closer to the Hb <11 g/dL (0.51) rather than the utility of target Hb >12 g/dL (0.58) in order for the target Hb>12 g/dL to be cost effective as defined by an ICER of £30,000 or less.

If the base-line rates of hospitalisations are changed from the assumption that rates are equivalent in each Hb target to the adjusted rates in the observational study 45, hospitalisation requires a cost. The national average unit cost of acute renal failure (£2,190) with upper (£2,983) and lower (£863) ranges of this unit cost was used in the sensitivity analysis of hospitalisation rates. ICERS with the lower and upper range of this unit cost were calculated to assess if there was an effect of the size of the cost of hospitalisation on the results. The Hb11-12 vs Hb<11 ICER decreased from 4,719 to 1,444 (hosp. cost £2,190), 3,719 (hosp. cost £863) and 84 (hosp. cost £2,983) further in favour of Hb11-12. The ICER Hb>12 vs Hb11-12 also decreased 54,822 to 41,481 (£2,190), 46,750 (£863), 38,333 (£2,983), however, these remain above a £30,000 cost-effectiveness threshold.

In probabilistic analysis, each parameter is assigned a distribution such as beta, normal, gamma etc. and random values from these distributions are used to derive cost-effectiveness results. The extent of uncertainty in the model is displayed in Figure 5. The scatter of the estimates indicate a high degree of uncertainty over the four quadrants. The cost-effectiveness acceptability curve (CEAC) (Figure 6) summarises the uncertainty of the results. For every value on the x-axis third-party payers are willing to pay, the probability the alternative is cost-effective is indicated on the y-axis. Between £20,000 to £30,000 willingness to pay threshold, the Hb target 11-12 g/dL has the highest probability of cost-effectiveness (0.378 to 0.365), suggesting Hb 11-12 g/dL is the best choice of the three alternatives. Even though the strategy has the highest probability of cost-effectiveness, there still is a large amount of uncertainty that could be improved with better data, especially compared to >12 g/dL.

The benefits in this model are assessed only for a 2-year period. This means life-time costs and benefits of treatments were not analysed. Also, the results were based on haemodialysis patients, rather than all CKD patients. If possible, randomised studies with target haemoglobin ranges corresponding to <11, 11-12 and >12 g/dL were selected. However, individuals will clinically respond differently to epoetin and there may be different distributions of achieved haemoglobin across the haemodialysis population with particular haemoglobin targets. The number of people who achieved the target was not taken into account in the selection of the data sources due to the limited reporting in the literature. The mean epoetin value for the <11 g/dL was based on an appropriate study target range, however there was a small number of patients 332. The 11-12 g/dL epoetin value was based on a European survey where guidelines suggests an 11-12 g/dL target. The target haemoglobin range in the 325 study was 1.5 g/dL higher than 12, which may have increased the amount of epoetin needed to reach higher than 12 while the quality of life data was from a lower haemoglobin (11.5-13.0 g/dL). The mean epoetin data sources combined three haemodialysis populations from the US, UK and Scandinavia potentially reducing the generalisability to the UK population. Therefore this is a preliminary analysis until further economic and clinical outcomes are measured.
The results are similar to the US study that found dosing epoetin to Hb >12.0 g/dL had unfavourable cost-effectiveness ratios. However, comparative target Hb ranges, costs included, such as cost of hospitalisation, haemodialysis care, renal transplantation, epoetin dosages and time horizon (life-time of patient) were different between the studies which may make comparing direct results inappropriate. Of note, the incremental cost per QALY gained in the 12.0-12.5 vs 11.0-12.0 g/dL comparison was approximately 11 times greater than the 11.0-12.0 vs. 9.5-10.5 g/dL in the US study. Whereas in this UK analysis the >12 vs 11-12 is approximately 9.5 times greater than the 11-12 vs <11 g/dL incremental cost per QALY gained.

**Conclusion**

The results suggest treating anaemia with a target Hb 11-12 g/dL is cost-effective in haemodialysis patients based on a £30,000 threshold. However, there is uncertainty in the results of the model from lack of certainty in the input parameters. Nevertheless, the results are relatively robust based on one-way sensitivity analyses and threshold analyses. This analysis is a simplified model of the costs and benefits of treating anaemia in the haemodialysis population and a variety of assumptions have been used in the base-line analysis. Therefore, the results should be interpreted correspondingly.
Appendix D: Health economic calculation: route of administration of ESAs

Background

Aim
To perform a cost-minimisation analysis based on equivalent effectiveness between intravenous (IV) and subcutaneous (SC) epoetin.

Methods

A cost-minimisation model was constructed from the perspective of the NHS. Cost analysis included epoetin, iron, administration and potential wastage. A meta-analysis of randomised controlled trials comparing IV and SC doses required to maintain target haematocrit or haemoglobin levels was performed to derive the average dose difference of IV and SC. Other resource use was estimated by expert opinion and the trials used in the meta-analysis.

Incremental cost = (C₁ – C₂)

Where:
C₁ = Estimated cost of IV epoetin therapy
C₂ = Estimated cost of SC epoetin therapy

Data Sources

Costs

SC Epoetin

Table 54. Unit cost of SC epoetin beta

<table>
<thead>
<tr>
<th>SC Epoetin beta</th>
<th>Units</th>
<th>Price (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC Epoetin beta</td>
<td>10000</td>
<td>77.93</td>
</tr>
<tr>
<td>SC Epoetin beta</td>
<td>20000</td>
<td>155.87</td>
</tr>
<tr>
<td>SC Epoetin beta</td>
<td>60000</td>
<td>467.61</td>
</tr>
</tbody>
</table>

Source: BNF 49

Subcutaneous injection of epoetin alfa is currently contra-indicated for use in patients with chronic kidney failure in the UK. The average cost per unit of SC epoetin used in cost calculations was £0.007793.

Other costs

Iron
Onlone only of the three studies included in the meta-analysis reported the average total amounts of iron administered per patient during all phases. No significant differences
in average total amount of parenteral iron dextran were found between the IV and SC groups within the study (1,683 ± 1,280 vs. 1,765 ± 1,342, p=0.65). Expert opinion indicated there would be an equivalent iron strategy in clinical practice regardless of the route of administration of epoetin. Therefore the cost difference of iron with IV or SC epoetin was assumed to be negligible.

Administration
Expert opinion suggested the same health professional would administer iv or sc epoetin, the healthcare setting would not need to be changed and wastage would be similar with either IV or SC administration. Two studies reported there was no significant difference in mean dialysis time 157 199. Therefore the cost difference of administration with IV or SC epoetin was assumed to be negligible.

Dose differences
Three randomised controlled trials 196 157 199 were used to derive the mean difference and 95% confidence interval of IV and SC dose in a fixed meta-analysis. Only studies receiving a 1++ or 1+ in the NICE levels of evidence hierarchy in the clinical effectiveness review and with n>7 were included. The average dose difference of patients treated with SC versus IV epoetin was 41.61 IU/kg/wk (95% CI 22.55 - 60.66) (p=0.000). Drug cost differences were calculated using the median unit cost in the base-case and the 95% confidence interval to calculate the range of cost-savings per week and per year.

Results
Based on a unit cost of £0.007793 per unit of epoetin and a 65 ± 10 kg patient, the average cost savings per patient with SC epoetin vs. IV epoetin was £21.08 ± £13.93 per week. The average yearly cost savings with SC epoetin was £1,100 ± £727 per patient.

Discussion
There are potential drug cost savings when using SC epoetin instead of IV epoetin to maintain target haematocrit or haemoglobin levels. These savings occur in supervised healthcare settings, however, self-administration in the patient’s home with SC epoetin is an alternative anaemia management strategy. Further evidence including delivery costs, gaining health professional time and treatment-related outcomes during self-management would be needed to assess different service provision strategies.

Darbepoetin is an alternative drug used in the management of anaemia in chronic kidney disease. Darbepoetin can be used by both the SC and IV routes of administration. However, due to the lack of data it was not included. When further data is available, this analysis could include the cost-effectiveness of darbepoetin SC vs. IV and darbepoetin vs. epoetin.

A potential consideration of SC vs. IV administration of epoetin that may vary on an individual level is patient preference due to potential pain at the injection site. One of the included randomised trials measured the discomfort during treatment 196. Of 96 patients
who had received both routes of administration, 74% preferred IV and 26% had no preference or preferred SC. Eight of 24 (33%) at the start of treatment with SC epoetin had pain at the injection site, however, only one of these patients had pain at the end of study (4 months). 31% of patients reported pain during placebo subcutaneous injection during the run-in period and only 18% reported pain during epoetin subcutaneous injection.

Conclusion

The subcutaneous route of administration of epoetin vs. intravenous route results in cost savings of approximately £1,100 + £727 per patient per year.
9 References


Ref Type: Generic

Ref Type: Generic


322. PRCA Global Scientific Advisory Board. PRCA. www.prcaforum.com. 2006. Ref Type: Electronic Citation


