NCGC National Clinical Guideline Centre

Final version, June 2015

Anaemia Management in Chronic Kidney Disease

Partial update 2015

This guideline was updated and merged with NICE guidelines on managing hyperphosphateamia (CG157) and the assessment and management of chronic kidney disease (CG182) in 2021. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021.
See the chronic kidney disease guideline on the NICE website for the guideline recommendations.

Clinical Guideline

Methods, evidence and recommendations

June 2015

Commissioned by the National Institute for Health and Care Excellence

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Partial update 2015

This is a partial update of the 2011 clinical guideline on Anaemia Management in Chronic Kidney Disease.

The sections new or updated in 2015 are:

- Guideline development group and scope
- Methodology
- Diagnostic tests for the prediction of response to iron therapy
- Concurrent illness
- Iron therapies
- Treatment of ESA resistance

All other sections and recommendations from the 2011 guideline remain unchanged.

The content of other sections has not been amended and we have integrated these new sections into the relevant chapters of the old publication. This has inevitably led to inconsistencies in style of write up for reviews.

New or amended sections of the guideline are highlighted in a pale orange box and have an 'Updated 2015' bar in the left hand margin.

Update 2015

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published 2006

Foreword

Chronic kidney disease (CKD) is not the most common cause of anaemia in the UK, but data from different sources suggest that nationally there are around 100,000 people with the combination of CKD and a low haemoglobin level. Anaemia in this context is important because it contributes significantly to the heavy symptom burden of CKD, and because it is potentially reversible with appropriate treatment, including erythropoietin. Erythropoietin is naturally produced by the kidneys and has been available in synthetic form for the treatment of anaemia of CKD since 1989, but it remains a fairly expensive product and its usage is not straightforward. Moreover, it will not necessarily be the only therapy required for optimal treatment. Against this background, the present guideline has been commissioned to address the appropriate management of anaemia of CKD for patients in the NHS.

The guideline has been produced using standard NICE methodology[242], and is therefore explicitly evidence-linked. Following a comprehensive literature search and evaluation of research papers, a Guideline Development Group (GDG) comprising clinical experts and patient and carer representatives assessed the evidence and used it to produce a detailed set of recommendations. This was no easy task, but one which the GDG have carried out diligently, thoroughly and with patient good humour. They have been a pleasure to work with and all at the National Collaborating Centre for Chronic Conditions are grateful to them.

The guideline recommendations cover many aspects of anaemia management in CKD, but some deserve emphasis. The thresholds at which treatment should be considered receive deserved attention, as do target values for haemoglobin. The GDG were clear that treatment, including administration of erythropoiesis stimulating agents, should be considered for all ages when there is the prospect of improving physical function and quality of life. The importance of correctly managing iron status is emphasised as well as the role of erythropoiesis stimulating agents. The GDG also stressed the importance of agreeing a detailed plan with patients regarding all aspects of delivery of treatment.

There is no doubt that symptoms would be improved in many patients with CKD if anaemia were to be managed optimally. We hope and expect that this guideline will make a significant contribution to improving the lives of the patients who suffer from this debilitating condition.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

Partial Update 2015

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

Why is anaemia important in patients with chronic kidney disease? Possible adverse effects of anaemia include reduced oxygen utilisation, increased cardiac output and left ventricular hypertrophy, reduced cognition and concentration, reduced libido and reduced immune responsiveness.

This guideline covers the management of anaemia in adults, children and young people with a clinical diagnosis of anaemia associated with CKD. It does not cover people with anaemia not principally caused by CKD. All parts of the care pathway are covered in the guideline. The guideline development group for this 2015 update considered the evidence in several areas that provide challenges for clinicians managing the anaemia of CKD. Recombinant human erythropoietin (also called 'EPO', or an erythropoietic stimulating agent or ESA) for treating anaemia of CKD provides a key tool in managing the anaemia of CKD. Some CKD patients with anaemia who are receiving an ESA are 'ESA resistant' – that is, their condition consistently fails to respond to the effects of the ESA. Patients with such a condition often receive large doses of ESA with or without blood transfusions, with limited benefits and at significant cost to healthcare. Many CKD patients receiving an ESA are admitted with an intercurrent illness – such as pneumonia – which may temporarily render them acutely hyporesponsive to that ESA. There is uncertainty about the management of these groups of patients, and these areas were considered in the update. The often limited trial evidence in nephrology, compared to other specialities, was again highlighted.

Over the past decade or more, attention has shifted to the role and management of iron deficiency in anaemia of CKD. In CKD patients there is often a complex inflammatory state which renders the diagnosis of iron deficiency difficult when using its standard markers, such as serum iron, serum total iron binding capacity or ferritin. In recent years evidence has been published on newer markers of iron deficiency and intravenous iron preparations. In this 2015 update, the guideline development group reassessed the diagnosis and management of iron deficiency in CKD, and made several recommendations in these areas.

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

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Acknowledgments [2011]

The development of this guideline was greatly assisted by the following people:

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Update 2015

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1 Introduction [2015]

1.1 Definition of anaemia

Internationally anaemia is defined as a state in which the quality and/or quantity of circulating red blood cells are below normal. Blood haemoglobin (Hb) 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 Hb 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. The units used in the UK have recently changed to grams per litre.

Conventionally anaemia is defined as a Hb concentration lower than the established cut off defined by the World Health Organization (WHO)[383], and different biological groups have different cut-off Hb values below which anaemia is said to be present. This cut-off figure ranges from 110 g/litre for pregnant women and for children between 6 months and 5 years of age, to 120 g/litre for non-pregnant women, and to 130 g/litre 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 Hb 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[141].

Table 1: Haemoglobin cut offs to define anaemia in people living at sea level[383]

Age or gender group	Hb below: (g/litre)
Children	
6 months to 5 years	110
5 to 11 years	115
12 to 14 years	120
Non-pregnant females >15 years	120
Men >15 years	130

In the Cardiovascular Health Study 8.5% 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[387].

In addition to gender, age, and pregnancy status, other factors influence the cut-off values for Hb concentration. These include altitude, race, and whether the individual smokes. Ethnicity may influence the cut-off values for Hb concentration. Data from the USA show that healthy people of African extraction of all age groups at all times, except during the perinatal period, have Hb concentrations 5–10 g/litre below those of white people, a difference independent of iron-deficiency and socioeconomic factors[81,130,159,269,278] Hb concentration increases in smokers because of the formation of carboxyhaemoglobin, which has no oxygen transport capacity[357].

1.2 Chronic kidney disease: definition and prevalence

NICE, other guideline bodies and renal societies all classify CKD in five stages (Table 2) defined by evidence of kidney damage, level of renal function as measured by glomerular filtration rate (GFR), and degree of albuminuria. The NICE clinical guideline on chronic kidney disease (CG 182) extended the previous advice on classifying CKD to include albuminuria when staging CKD. The basic CKD stages (without the additional albuminuria classification) are shown for the reader in Table 2. For the detailed classification refer Glossary, section 8.2.

Table 2: Stages of chronic kidney disease

Stage	GFR (ml/min/1.73 m^2)	Description
1	>90	Normal or increased GFR **with** other evidence of kidney damage
2	60–89	Mild reduction in GFR (related to normal range for young adults), **with** other evidence of kidney damage
3a	45-59	Mild to moderate reduction in GFR
3b	30–59	Moderate to severe reduction in GFR
4	15–29	Severe reduction in GFR
5	<15	Established renal failure or end stage renal disease

Stage 5 CKD may be described as established renal failure or end stage renal disease, and is CKD which has progressed so far that renal replacement therapy (RRT – that is regular dialysis treatment or kidney transplantation) will soon 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.

1.2.1 Prevalence of anaemia in patients with chronic kidney disease

Anaemia begins to develop early in the course of CKD. NHANES III found lower levels of kidney function to be associated with lower Hb levels and a higher prevalence and severity of anaemia[73].

Table 3: NHANES III data

eGFR (ml/min/1.73 m^2)	Median Hb in men (g/litre)	Median Hb in women (g/litre)	Prevalence of anaemia[a]
60	149	135	1%
30	138	122	9%
15	120	103	33%

(a) Hb ≤120 g/litre in men, Hb ≤110 g/litre in women.

The UK information concerning the prevalence of anaemia in patients with CKD comes from two studies. The prevalence of diagnosed CKD, predicated by serum creatinine levels of more than or equal to 130 µmol/litre in women and more than or equal to 180 µmol/litre 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/1.73 m^2 (range, 3.6 to 42.8 ml/min/1.73 m^2)[154]. Data for Hb levels were available for 85.6% of patients. Mean Hb concentration was 121±19 g/litre: 49.6% of men had Hb levels less than 120 g/litre and 51.2% of women had levels less than 110 g/litre. Furthermore, in 27.5% of unreferred patients identified, the Hb level was less than 110 g/litre, equivalent to nearly 90,000 of the population based on 2001 Census population 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, Hb level was weakly correlated with eGFR ($r=0.057$, $p<0.001$)[85]. 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 Hb level less than

120 g/litre in men and post-menopausal women and less than 110 g/litre in pre-menopausal women, was 15.3%, Hb level was less than 110 g/litre in 3.8%, equivalent to over 108,000 of the population based on 2001 Census population figures.

1.2.2 Diabetes, CKD and anaemia

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 erythropoietin concentrations[151,176]. Ishimura et al[151] demonstrated that when those with Type 2 diabetes and CKD are compared with those with non-diabetic CKD, the Type 2 diabetics were significantly more anaemic. Thomas and colleagues demonstrated that at all levels of GFR, anaemia was more prevalent in those with diabetes compared with the general population[354], that with increasing albuminuria the prevalence of anaemia was higher at each level of renal function[353], and that levels of erythropoietin were inappropriately low in those with anaemia[352].

1.2.3 Causes of anaemia other than chronic kidney disease

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.

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[142,164,277]. Iron-deficiency is the cause in 15% to 36% of cases and recent bleeding in 7.3%. Vitamin B12 or 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%.

1.2.4 Pathogenesis of anaemia associated with chronic kidney disease

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. 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 (for example, parathyroid hormone, inflammatory cytokines), reduced half-life of circulating blood cells, and deficiencies of folate or Vitamin B12.

Hepcidin is a small peptide produced by the liver, which inhibits iron absorption and also its release from stores. Inflammation increases hepcidin production, and this is thought to contribute to anaemia of CKD. The GDG were aware that serum hepcidin assays are carried out in research settings, but noted that the evidence to date suggested that this assay does not provide sufficient clinical utility for predicting response to intravenous iron. There is an important impact of malnutrition and inflammation, also called the malnutrition-inflammation-atherosclerosis (MIA) syndrome, on anaemia in CKD. Data suggests that this combination of conditions contributes to ESA resistance, and is associated with increased mortality.[270,293] Even a poor **early** response to an ESA and early relative ESA resistance are associated with increased morbidity and mortality.[326] This is further discussed in the chapter on ESA resistance.

1.2.5 Current anaemia management challenges in CKD in the United Kingdom

The 2013 Renal Registry Report[351], reviewing 2012 data, showed that about 7000 patients started RRT in the UK, representing a yearly incidence of 108 patients per million population. In 2012, in the UK, there were about 55,000 patients receiving renal replacement therapy during 2003, a prevalence of 861 per million population. Of these, 50% had a functioning transplant, 43% were on haemodialysis, and 7% on peritoneal dialysis. Interestingly the number needing RRT has increased by about 65% since 2000. This represents a significant need for anaemia management in UK healthcare.

Late presentation within 90 days of needing RRT presents various challenges, including in anaemia management. Such late presentation has now fallen below 20% of all new RRT patients. Approximately one-third of late presenting patients in 2012 had a Hb of 100 g/litre or more, compared to about 80 to 85% of all prevalent dialysis patients.

Red cell transfusion use remains a little discussed area of anaemia management in CKD. Published data from the United States suggests that it is not uncommon amongst CKD patients not on dialysis.[119,135] That this happened even in younger patients is of concern, in that it risks sensitisation and a reduced chance of renal transplantation. This is discussed in the updated guideline.

Modern anaemia management practices are reflected in the median Hb achieved in the UK dialysis population, which is about 110 g/litre. However, the UK Renal Registry data continues to show significant differences in 'anaemia of CKD performance' at a local level.[351] Data from the DOPPS consortium[283] studied Hb variation in over 25,000 haemodialysis patients across 12 countries. Hb variability was closely linked to the local anaemia management practices, and importantly showed a strong positive association with mortality. This clearly indicates that Renal centres need to do more to standardise and individualise their approach to anaemia management in patients with CKD. Recent work confirms older data that reducing human decision making by using a computer based algorithm improves anaemia outcomes in end stage renal disease.[201] Unsurprisingly, an individualised algorithm applied to each patient also improves anaemia outcomes.[133] One obvious interpretation is that careful attention to guidelines and their optimal implementation for each patient will reap rewards.

In conclusion, despite much progress in recent years there remain significant challenges in the management of anaemia in CKD for healthcare in the UK. Nephrology continues to have a need for randomised clinical trials (RCTs) in this area, reflecting its historically poor performance in carrying out trials. RCTs are the 'life blood' of any NICE guideline, and the guideline development group was frustrated at times by the lack of such evidence. Nevertheless, the work of the group in this update was able to highlight important areas for new guidance.

1.3 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 Summary of Product Characteristics 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.

2 Methodology [2006]

2.1 Aim

The aim of the National Clinical Guideline Centre (NCGC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) that:

- offers best clinical advice for anaemia management in chronic kidney disease (AMCKD)
- 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.

2.2 Scope

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 of 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 the National Institute for Health and Clinical Excellence (NICE)[241,242]. The full scope is shown in Appendix V.

The partial update 2011 scope is also shown in Appendix V.

2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with anaemia of CKD and their parents and carers
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with anaemia of CKD

The NCGC was keen to ensure the views and preferences of people with anaemia of CKD and their parents and 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 (GDG)
- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.

2.5 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.

2.6 Other work relevant to the guideline

The NCGC and NICE are developing a clinical guideline on chronic kidney disease (publication is expected in 2008).

NICE has published technology appraisal guidance on erythropoietin for anaemia induced by cancer treatment. This is available from www.nice.org.uk

2.7 Background

The development of this evidence-based clinical guideline draws on the methods described by the NICE Guideline development methods manual[242] and the methodology pack[239] specifically developed by the NCGC for each chronic condition guideline. The developers' role and remit is summarised in Table 4.

Table 4: Role and remit of the developers

NCGC	The NCGC was set up in 2009 and is housed within the Royal College of Physicians (RCP). The NCGC undertakes commissions received from the National Institute for Clinical Excellence (NICE). A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCGC.
NCGC Technical Team	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members: GDG Chair GDG Clinical Advisor Information Scientist Research Fellow Health Economist Project Manager.
Guideline Development Group	The GDG met monthly for 12 months (January to December 2005) and comprised a multidisciplinary 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:

	NCGC Director NCGC Assistant Director NCGC 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[242]. A register is available from the NCGC for inspection upon request: enquiries@ncgc.ac.uk	

2.8 The process of guideline development

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

- developing clinical evidence-based questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- grading the evidence statements and recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix U.

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 supplemental papers to inform detailed health economic work (for example 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 U for literature search details.

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:

- NICE methodology as detailed in the 'Guideline development methods – information for National Collaborating Centres and guideline developers' manual[242].
- NCGC quality assurance document and systematic review chart.

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.

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 on which to formulate recommendations[383]. The criteria for grading evidence and classifying recommendations are shown in Table 5.

Evidence tables are available online at http://www.ncbi.nlm.nih.gov/books/NBK65515/

Table 5: Grading the evidence statements and recommendations

Levels of evidence			**Classification of recommendations**
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* Level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1−	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation	
2++	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.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results. *or* Extrapolated evidence from 1++ or
2+	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.		

			1+.
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* Extrapolated from 2+ *or* Formal consensus.
		GPP	A good practice point (GPP) is a recommendation based on the experience of the GDG.
Diagnostic study level of evidence and classification of recommendation was also included[242].			

Agreeing the recommendations

The sign-off workshop employed formal consensus techniques[240] 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[242].

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 provide a synthesis of the evidence base and usually describe 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 recommendations sets out the GDG decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- Recommendations provide stand alone, action-orientated recommendations.
- Evidence tables are not published as part of the full guideline but are available online at http://www.ncbi.nlm.nih.gov/books/NBK65515/**.**These describe comprehensive details of the primary evidence that was considered during the writing of each section.

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[242]. The registered stakeholders for this guideline are detailed on the NICE website, see www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

Table 6: Versions of this guideline

Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at **www.nice.org.uk/guidance**
NICE version	Documents the recommendations without any supporting evidence. Available at **www.nice.org.uk/guidance**
Quick reference guide	An abridged version. Available at **www.nice.org.uk/guidance**
Information for the public	A lay version of the guideline recommendations. Available at **www.nice.org.uk/guidance**

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 by 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 4 years after publication[242].

2.9 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 NCGC 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.

2.10 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.

Methodology [2011]

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009[244].

2.11 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome). This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). The PICO questions were drafted by the NCGC technical team, refined and validated by the GDG and based on the key clinical areas identified in the scope (Appendix V). Further information on the outcome measures follows this section. See Table 7.

Table 7: Review questions and outcomes

Chapter	Review question	Outcomes
4	In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?	• All-cause mortality. • Cardiovascular mortality. • Increased hospitalisation. • Stroke. • Myocardial infarction. • Left ventricular hypertrophy/left ventricular mass index. • Quality of life indices. • Progression of CKD in non-dialysis patients.
6.9	What should be the aspirational haemoglobin (Hb) target range for patients undergoing treatment for anaemia in CKD?	• All-cause mortality. • Cardiovascular mortality. • CKD progression (studies with non-dialysis patients). • Access thrombosis (for studies with haemodialysis patients). • Stroke. • Myocardial infarction. • Hypertension/blood pressure control. • Left ventricular hypertrophy/left ventricular mass index. • Reduction in transfusion requirements. • Hb variability. • Quality of life indices.

2.12 Searching for evidence

2.12.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence from 2005 onwards within the published literature in order to answer the review questions as per the Guidelines Manual 2009[244]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. Searches were conducted in core databases, MEDLINE, Embase, Cinahl and the Cochrane Library. All searches were updated on 8th July 2010. No papers after this date were considered. Search strategies were checked against search strategies in the original guideline, reference lists of relevant key papers, search strategies in other systematic reviews and asking the GDG for known studies. Searching for grey literature or unpublished literature was not undertaken. The questions, the study types applied, the databases searched and the years covered can be found in Appendix U.

2.12.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within the published literature relevant to the review questions published since the original guideline. The evidence was identified by conducting a broad search relating to anaemia management in chronic kidney disease in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases from 2005 onwards (the cut-off date for the original guideline was 28th September 2005). Additionally, the search was run in Medline and Embase, with a specific economic filter, from January 2009, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix U. All searches were updated on 8th July 2010. No papers published after this date were considered.

2.12.3 Request for additional data

Many studies in the optimal Hb review (Section 6.9) reported SF-36 results but did not provide full numerical data for all eight domains. In order to provide data for meta-analysis and mapping of SF-36 to EQ5D for use in the economic analysis, numerical data for all eight domains was requested for studies that either reported the significance of the results but did not report the numerical data or where results for only certain domains on the SF-36 were reported. In addition the authors of one study that reported that SF-36 data was collected and would be reported separately was contacted. The clinical advisor on behalf of the NCGC contacted the lead authors.

Lead authors for six studies in the predialysis population were contacted for further information:

- Four studies[96,279,301,304] that reported some results for SF-36
- One study[307] that reported results graphically at the end of a stabilisation period (4 months) and non-numerically at the end of the following maintenance phase
- One study[192] that reported that SF-36 data was collected and would be reported separately.

Data for two of these six studies[155,302] was provided by the sponsors of the studies.

Lead authors for two dialysis studies were contacted for further information:

- Both studies reported some results for SF-36[41,272]

Data for one of these two studies[20] were provided by the sponsor of the study[20].

2.13 Evidence of effectiveness

The Research Fellow identified potentially relevant studies for each review question from the search results by reviewing titles and abstracts – full papers were then obtained.

Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix AA).

Relevant studies were critically appraised using the appropriate checklist as specified in the Guidelines Manual 2009[244].

Key information about the study's methods and results was extracted into evidence tables (evidence tables are included in Appendix BB).

Summaries of the evidence by outcome were generated (and included in the relevant chapter write-ups).

Where appropriate randomised studies were meta-analysed, and reported in GRADE profiles (for clinical studies) – see below for details.

2.13.1 Inclusion/exclusion

See the review protocols in Appendix AA for full details.

2.13.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes. The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio using the generic invariance method on the Cochrane Review Manger (RevMan5) software. In order to enable pooling with studies that did not report the outcome as a time-to-event, an estimate of the hazard ratio was calculated from the risk ratios using a Microsoft Excel spreadsheet[356]. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, predefined subgroup analyses for co morbidities (diabetes, heart failure) was carried out. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data (if the reason for lost to follow-up was not due to renal replacement therapy) or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

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

The means and standard deviations of continuous outcomes were required for meta-analyses. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if the p value was reported as "p ≤0.001", the calculations for standard deviations was based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (September 2009)[5] 'Missing standard deviations' were applied as the last resort.

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

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software. Studies were not combined in a meta-analysis for cohort studies. Heterogeneity between trials was assessed by visual inspection of forest plots. Where appropriate, sensitivity analyses were carried out on the basis of study quality and results were reported as ranges.

2.14 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic evidence- quality assessment" table includes details of the quality assessment while the "Clinical /Economic - results" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent. Each outcome was examined separately for the quality elements listed and defined in Table 8 and each graded using the quality levels listed in Table 9. The main criteria considered in the rating of these elements are discussed below (see section 2.14.1, Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 10). The GRADE toolbox is currently designed only for randomised trials and observational studies and hence does not apply to prognostic or diagnostic studies.

Table 8: Descriptions of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.

Quality element	Description
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 9: Levels for quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 10: Overall quality of outcome evidence in GRADE

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

2.14.1 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

A quality rating was assigned, based on the study design. RCTs start as HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.

The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.

The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections.

2.14.2 Study limitations

The main limitations for randomised controlled trials are listed in Table 11.

Table 11: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • carry-over effects in cross-over trials • recruitment bias in cluster-randomised trials

2.14.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

2.14.4 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

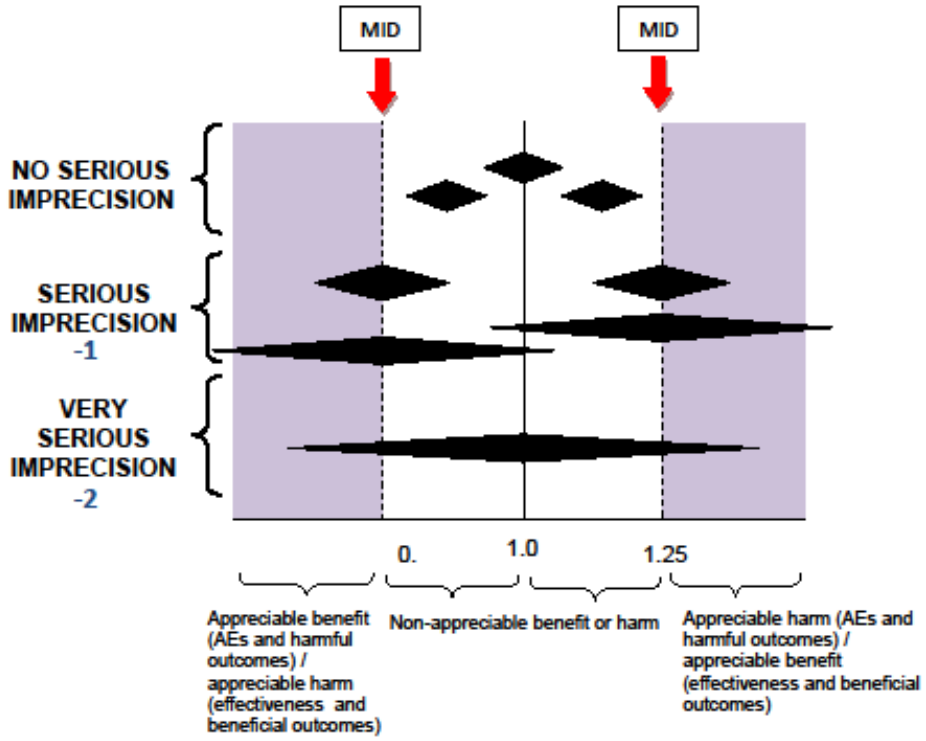
2.14.5 Imprecision

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as outlined in Table 12, an illustrative explanation of imprecision is shown in Figure 1.

Table 12: Criteria applied to determine precision

Dichotomous and continuous outcomes
1. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) does not cross the threshold for appreciable benefit or harm defined as precise Rating for precision: 'no serious imprecision'
2. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) If the 95% confidence interval crosses either minimal important difference (MID) threshold, defined as imprecise Rating for precision: 'serious'
3. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: a) crosses both the line of appreciable benefit and harm, defined as imprecise Rating for precision: 'very serious'

Figure 1: An illustrative explanation of imprecision



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms.

The MIDs for the outcomes in the guideline are shown in Table 13. The MID's for the outcomes were based on the advice from the clinical advisor, Chair and GDG for the guideline.

Table 13

Outcome	Relative risk reduction
All-cause mortality	5%
CV mortality	5%
Progression of CKD	5 ml/min
Access thrombosis	20%
Transfusion requirements	25%
Stroke	5%
MI	5%
Hypertension	10%
Change in LVMI	25%

For quality of life on the SF-36 there were no published studies reporting the minimal important difference for all the SF-36 domains in the CKD population. One study[48] which used a dataset of patients with chronic conditions (cardiovascular, musculo-skeletal, respiratory, uro-genital [including kidney disease], and other disorders) recommended a MID of 5 points on the vitality domain of the SF-36 in patients groups with an average score approaching one standard deviation below the

general population average. One study[41] reported an increase of 7.2 points was a clinically meaningful increase in the score on the physical-function scale. As there was limited information on MIDs for all domains of the SF-36 in the literature, a distribution-based method[298] of estimation of MID was utilised where MID is approximately 1/2 of the standard deviation or is approximately one standard error of measurement.

2.15 Evidence of cost-effectiveness [2011]

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

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

2.15.1 Literature review [2011]

The Health Economist:

- Identified potentially relevant studies for each review question for the update from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[244] .
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix BB).
- Generated summaries of the evidence .

2.15.2 Inclusion/exclusion [2011]

Full economic evaluations (cost-effectiveness, cost¬–utility, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence. The same population and intervention criteria were applied as in the clinical review.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-Organisation for Economic Co-operation and development [OECD] country).

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

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix BB)[244] and the health economics research protocol in Appendix AA.

2.15.3 Undertaking new health economic analysis [2011]

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See the Health Economic Appendix W for details of the health economic analysis undertaken for the guideline.

Methodology [2015]

This chapter sets out, in detail, the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[245]

2.16 Developing the review questions and outcomes

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

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of five review questions were identified as part of this update.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 14: Review questions

Chapter	Type of review	Review questions	**Outcomes**
4.3	Diagnostic 1a	In people with suspected (or under investigation for) anaemia of CKD, what is the comparative clinical and cost effectiveness of the following tests or combination of tests at predicting response to iron, when each is followed by the appropriate treatment in order to improve patient outcomes?	Critical outcomes: • ESA use to maintain target haemoglobin (Hb) • Number of patients responding to iron therapy • Quality of life
4.3	Diagnostic 1b	What is the accuracy of the following tests, or combination of tests, at predicting response to iron therapy in patients with CKD?	Critical outcomes: • Sensitivity Important outcomes: Specificity • Positive predictive values • Negative predictive values. • AUC
6.12	Intervention 2	What is the optimal management of anaemia of CKD in hospitalised patients who are on ESAs and have a concurrent acute infectious illness?	Critical (treatment-related outcomes) • Improvement in Hb levels • Number of units transfused • Average ESA use per patient Important • Length of hospital stay • In hospital mortality • HRQoL
6.15	Intervention 3a	What is the most clinically and cost effective and safest dose, frequency, preparation and	Critical (those related to haematological efficacy)

Chapter	Type of review	Review questions	**Outcomes**
		route of administration of iron for people with anaemia of CKD with iron deficiency prior to receiving ESA treatment?	Correction of anaemia – efficacy/Hb response • % achieving target Hb • Time to achieve target Hb • Mean change of Hb from baseline • Increase in Hb >10 g/litre or other target Epoietin/ESA • Numbers of patients needing to begin ESA therapy or receive one or more blood transfusions. Important • Mean change from baseline/numbers achieving target (ferritin, TSAT, CHr) • All-cause mortality (6 months and 12 months) • Compliance • Patient preference • Quality of life
6.15	Intervention 4a	What is the most clinically and cost effective and safest dose, frequency, preparation and route of administration of iron for people with anaemia of CKD with iron deficiency receiving ESA treatment?	Critical (those related to haematological efficacy) Correction of anaemia – efficacy/Hb response • % achieving target Hb • Time to achieve target Hb • Mean change of Hb from baseline • Increase in Hb >10 g/litre or other target Epoietin/ESA • Numbers of patients needing one or more blood transfusions. Important • Mean change from baseline/numbers achieving target (ferritin, TSAT, CHr) • All-cause mortality (6 months and 12 months) • Compliance • Patient preference • Quality of life
6.15	Intervention 3b and 4b	What is the safest dose, frequency, preparation and route of administration of iron for people with anaemia of CKD with iron deficiency prior to and during ESA treatment?	Adverse effects • GI complications • Hypersensitivity reactions • General investigator-considered treatment-related

Chapter	Type of review	Review questions	**Outcomes**
			adverse events. • Number of patients needing to cease oral or IV supplements because of adverse effects
7.5	Intervention 5	In people with chronic ESA-resistant anaemia of CKD, what is the clinical and cost effectiveness of treating with high-dose ESA compared with blood transfusion?	Critical (treatment-related outcomes) • Improvement in Hb levels (mean Hb in the course of the study) • Number of units transfused • Average ESA use per patient Important • Morbidity, including: ○ Hospitalisation - admission to hospital (might not always be reported) ○ HRQOL • Mortality – 6 months and 1 year (if see a change earlier than 6 months it is unlikely to be due to the strategy used) • Side effects/adverse events ○ Transfusion-related side effects ○ ESA-related side effects

2.17 Searching for evidence

2.17.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within The guidelines manual (2012).[245] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. All searches were updated on 14 August 2014. No papers published after this date were considered.

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

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

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

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

2.17.2 Health economic literature search

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

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

2.18 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 2:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual (2012).[245] For diagnostic questions, the QUADAS-2 checklist[363,376] was followed (see Appendix F of The guidelines manual [2012]).
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings.
    - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
    - Observational studies: data were presented as a range of values in GRADE profiles.
    - Diagnostic studies: A diagnostic meta-analysis was conducted for two tests, (transferrin saturation [TSAT], less than 20% and serum ferritin [SF], less than 100 micrograms/litre), as data was available from five or more studies at a particular threshold. For the remainder of the tests, data were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in Receiver Operating Curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively (given data were reported at the same thresholds).

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

Figure 2: Step-by-step process of review of evidence in the guideline

2.18.1 Inclusion and exclusion criteria

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

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

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

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

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

2.18.2 Methods of combining clinical studies

2.18.2.1 Data synthesis for intervention reviews

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

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as mean change of Hb from baseline were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics, and 95% confidence interval (CI) or standard error (SE); this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the SE for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Therefore, aspects of quality assessment, such as imprecision of effect, could not be assessed for evidence of this type.

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

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

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

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

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the SE was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and SE using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value is reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not

available, then the methods described in Section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

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

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

2.18.2.2 Network meta-analysis

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

2.18.2.3 Data synthesis for diagnostic meta-analysis and test accuracy reviews

Data and outcomes

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

Data synthesis

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

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

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

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

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

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

2.18.3 Type of studies

For most intervention reviews in this guideline, parallel RCTs were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

For diagnostic reviews, RCTS and observational studies (case control studies were excluded a priori) were included.

2.18.4 Appraising the quality of evidence by outcomes

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

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 15. Each element was graded using the quality levels listed in Table 16. The main criteria considered in the rating of these elements are discussed below (see Section 2.18.5, Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 17).

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

Table 15: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 16: Levels of quality elements for downgrading evidence in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 17: Overall quality of outcome evidence in GRADE

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

2.18.5 Grading the quality of clinical evidence

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

1. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results

showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points, respectively.

3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted, respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

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

2.18.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 18.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

The GDG accepted that investigator blinding in studies with patients on haemodialysis or peritoneal dialysis was impossible and participant blinding was also impossible to achieve in most situations. Nevertheless, open-label studies were downgraded to maintain a consistent approach in quality rating across the guideline and the recognition that most of the important outcomes considered were subjective or patient reported (for example, gastrointestinal adverse events) and therefore, highly subjected to bias in an open label setting.

Table 18: Risk of bias in RCTs

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes

2.18.6.1 Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist was used (see Appendix F in The guidelines manual [2012][245]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 3):

- patient selection

- index test
- reference standard
- flow and timing.

Figure 3: Summary of QUADAS-2 checklist

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: QUADAS-2 website, University of Bristol[363]

Optional domain, multiple test accuracy is applicable when a single study examined more than 1 diagnostic test (head-to-head comparison between 2 or more index tests reported within the same study). This optional domain contains 3 questions relating to risk of bias:

- Did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients?
- Were index tests conducted within a short time interval?
- Are index test results unaffected when undertaken together on the same patient?

2.18.7 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined, and sensitivity and subgroup analyses were performed as prespecified in the protocols (Appendix C).

When heterogeneity was evident (chi-squared $p<0.1$, I-squared inconsistency statistic of more than 50%, or evidence from examining forest plots), but no plausible explanation could be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention was associated with

benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

2.18.8 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

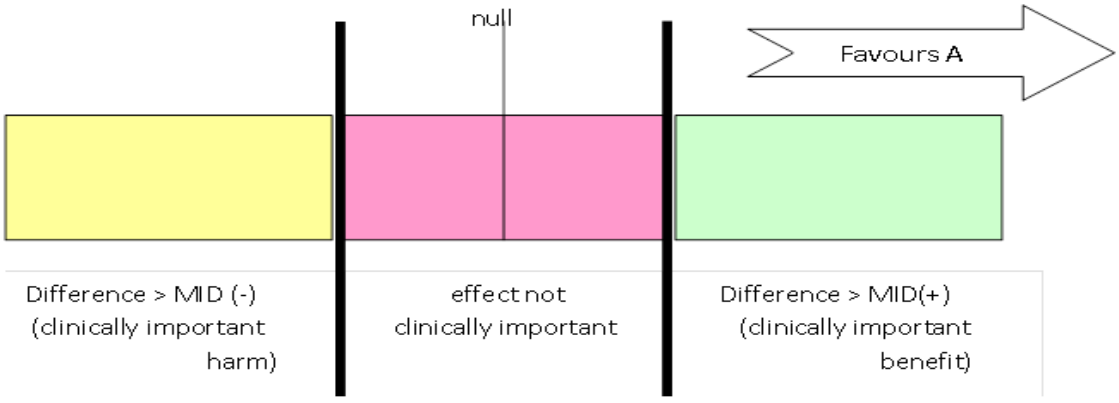
2.18.9 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision making, considering each outcome in isolation. Figure 4 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 4: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is

considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community of Anaemia in Chronic Kidney Disease but they confirmed the absence of research in the area. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to a RR clinically important threshold of 0.75 or 1.25 respectively. This default MID was used for all the dichotomous outcomes in the interventions evidence reviews.

Where continuous MIDs were required, the default MID values of 0.5 multiplied by the standard deviation (SD) of the baseline values were used except for one outcome (Mean change of Hb from baseline), where the GDG considered a change of 10 g/litre to be a minimal clinically important difference.

2.18.10 Assessing clinical importance

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

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

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

2.18.11 Evidence statements

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

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

- a description of the overall quality of evidence (GRADE overall quality).

2.19 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected net health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[245] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

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

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

2.19.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual (2012).[245]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

2.19.1.1 Inclusion and exclusion criteria

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

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

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

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The guidelines manual [2012][245] and the health economics review protocol in Appendix D of this guideline).

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

2.19.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual (2012).[245] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 19 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[265]

Table 19: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[245]

2.19.2 Undertaking new health economic analysis

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

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

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[246]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

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

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

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

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

a. haemodialysis and
b. pre-dialysis and peritoneal dialysis.

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

2.19.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[243] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

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

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues about the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[243]

2.19.4 In the absence of economic evidence

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

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

2.20 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

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

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

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, and recommendations made in other relevant guidelines, patient preferences and equality issues. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 2.20.1 below).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular

intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effects and others are not. In these circumstances, the recommendation is generally weaker, although, it may be possible to make stronger recommendations about specific groups of patients.

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

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in The guidelines manual [2012][245]).

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

2.20.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

2.20.2 Validation process

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

2.20.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

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

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

2.20.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Complete list of recommendations

1

2

3.2 Audit criteria [2006, updated 2011]

Table 20: Audit criteria

Key priority for implementation	Criterion	Exception
ESA therapy should be clinically effective, consistent and safe in people with anaemia of CKD. To achieve this, the prescriber and patient should agree a plan which is patient-centred and includes: • provision of a secure drug supply • flexibility of where the drug is delivered and administered • lifestyle and preferences • cost of drug supply • desire for self-care where appropriate • regular review of the plan in light of changing needs.	3. % of patients with ACKD receiving anaemia treatment who are receiving ESAs, with a plan recorded as specified.	
In people with anaemia of chronic kidney disease, treatment should maintain stable haemoglobin (Hb) levels between 10 and 12 g/dl for adults and children aged over 2 years, and between 9.5 and 11.5 g/dl in children aged under 2 years, reflecting the lower normal range in that age group. This should be achieved by: • Considering adjustments to treatment, typically when Hb levels are within 0.5 g/dl of the range's limits. • Taking patient preferences, symptoms and comorbidity into account and revising the aspirational range and action thresholds accordingly.	4. % of patients with diagnosed ACKD who have received treatment for 3 months or longer and, at the time of a cross-sectional audit, have Hb levels between 10 and 12 g/dl for adults and children aged over 2 years, or between 9.5 and 11.5 g/dl in children aged under 2 years.	Patients who have underlying causes for poor response (see section 1.2.4), patients who are in the induction phase of their treatment.
Patients receiving ESA maintenance therapy should be given iron supplements to keep their: • serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients, and either • the transferrin saturation level above 20% (unless ferritin > 800 µg/l) or • percentage hypochromic red cells (%HRC) less than 6% (unless ferritin > 800ug/l). In practice it is likely this will require i.v. iron.	5. % of patients with diagnosed ACKD and on maintenance therapy with ESAs who, at the time of a cross-sectional audit, have: • serum ferritin between 200 and 500 µg/l in both haemodialysis patients and non-haemodialysis patients and either • The transferrin saturation level above 20% (unless ferritin >800 µg/l) or • Percentage hypochromic red blood cells (%HRC) less than 6% (unless ferritin >800ug/l).	

4 Diagnostic evaluation and assessment of anaemia

4.1 Diagnostic role of Hb levels [2006]

4.1.1 Clinical introduction [2011]

Why is the haemoglobin level important in patients with CKD? Possible adverse effects of anaemia include reduced oxygen utilisation, increased cardiac output and left ventricular hypertrophy, 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. What is incontrovertible is that since the introduction of human recombinant erythropoietin for treatment of CKD-related anaemia over 2 decades ago we have had the tools to significantly influence anaemia management. The phenotype of the kidney patient with haemoglobin levels between 5-8 g/dL, rendered massively iron over-loaded and virtually un-transplantable as a result of multiple transfusions, has thankfully become unrecognisable. Attention has shifted from treatment of severe anaemia in dialysis patients to prevention of anaemia non-dialysis and to correction of anaemia to higher levels of haemoglobin.

It is well established that haemoglobin levels fall as kidney function declines but there is significant heterogeneity at each level of kidney dysfunction. Although normal values for haemoglobin in the general population differ by gender this has not been addressed in most study designs of anaemia in kidney disease. Observational data suggest that lower haemoglobin values are associated with increased cardiovascular abnormalities/events, increased hospitalisation, increased mortality, increased transfusion requirements and reduced quality of life. Major criticisms though have been the heterogeneity of such studies and the variation in adjustment for confounders. We do not have randomised controlled trials designed to assess the level of haemoglobin at which we should intervene with treatment but we do have treatment dilemmas. We know from clinical practice that not all patients will necessarily benefit from treatment so at what level of haemoglobin should we consider intervention with anaemia treatment? Should this level differ by age, gender or ethnicity? Should we adopt differing strategies dependent on whether patients are non-dialysis or already receiving renal replacement therapy?

The GDG agreed to address the following question: *In patients with chronic kidney disease, what haemoglobin (Hb)/haematocrit (Hct) levels are associated with adverse outcomes and what are the effects of a) age b) gender c) ethnicity?*

4.1.2 Methodological introduction

A literature search identified longitudinal,[150,287,375,381] before and after[143,222,226,317] and cohort[70,193,196,204] studies, conducted predominantly in haemodialysis patients.

Four studies[92,162,186,227] had methodological limitations and were excluded from evidence statements.

Notable aspects of the evidence base were:

- 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[226].
- Only two studies included populations over 80 years old[150,196].

- Not all studies reported gender and ethnicity of the participants. Some studies included predominantly male[222,317] or predominantly white participants[70,196] or predominantly male and white participants[92,193]. One study included a population that was 67% African American[150].
- The number of study participants varied greatly, ranging between 7 and over 60,000.

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 Methodological introduction [2011]

The GDG noted a change in terminology for the 2011 update concerning predialysis to nondialysis.

A literature search was undertaken to identify papers published from September 2005 onwards. Eight cohort studies[127,179,187,191,218,285,374,380] in nondialysis, haemodialysis and transplant patients were included. Studies not meeting the inclusion criteria were excluded.

Notable aspects of the evidence base:

- No studies were found which reported the interaction of age, gender and ethnicity with Hb/Hct levels.
  - One study[179] included only male patients with subgroup analyses for age and ethnicity. The results were only presented on a forest plot and numerical data were not reported.
- The mean age, where reported, ranged from 51 years[380] to 72 years[187]; one study[191] reported 29% of the included patients were over 75 years.
- The ethnicity of the patients included in the studies comprised mainly of those classified as white. One study[179] reported patients with higher Hb levels were likely to be 'white'.

The outcomes considered in the review are:

- Left ventricular hypertrophy
- Hospitalisation
- Mortality
- Composite outcome (all cause mortality, stroke and MI)
- Cardiac events
- Quality of life
- Stroke
- Progression of CKD

4.1.4 Evidence statements [2006, updated 2011]

These evidence statements are grouped by outcome measure per sub-population of anaemia patients.

Left ventricular hypertrophy

Predialysis patients

In a 1-year study[227] (n=318), 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 left ventricular hypertrophy (LVH) (OR 1.32, 95% CI 1.1 to 1.59, p=0.004). (Level 2+)

A decrease in LV mass index (p<0.01) was observed after raising haematocrit (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)[143]. Similarly, in another study[287] (n=11) 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)

In two studies,37,41 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 months37 and from 23.6 ± 0.5% (Hb ~ 7.8 g/dl) to 39.1 ± 0.8% (Hb ~ 13 g/dl) at 12 months41 found no changes in LV end-diastolic/systolic diameters, interventricular septum thickness, LV posterior wall thickness over 6 months37 or over 12 months.41 (Level 3)

Haemodialysis patients

In a 12 month study[317] 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 210 g. In the same study[317], no significant changes were observed in echocardiography measurements of LV posterior wall, interventricular septum or mean wall thickness. (Level 3)

In a small study[222] (n=7), 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 ($p<0.05$). However, there was no change in mean arterial pressure. (Level 3)

There were no new relevant studies identified reporting left ventricular hypertrophies in the rapid update review. [2011]

Hospitalisation

Haemodialysis patients

A cohort (n=66,761), with data stratified into increasing Hct levels and compared with an Hct level of 33 to 35% over a 1-year follow-up period[70] found the following:

Table 21: Summary data from study[70] (Level 2+)

Hct (%)	**<30**	**30 to 32**	**33 to 35 (Ref)**	**36 to 38**	**≥39**
Hb (g/dl)	**<10**	**10-10.7**	**11 to 11.7 (Ref)**	**12 to 12.7**	**≥13**
RR of all-cause hospitalisation	1.42	1.21	1	0.78	0.84
RR of hospitalisation from cardiac causes	1.3	1.17	1	0.75	NS
RR of hospitalisation from infections	1.76	1.3	1	0.82	0.62

RR = relative risk; NS = not significant

In a 2.5-year follow-up study[196], participants (n=50,579) were stratified into increasing Hct levels and compared with patients with the arbitrary reference of Hct 34 to 36% (n=22,192), seeTable 22 to Table 25.

Table 22: Adjusted relative risk of first hospitalisation due to any cardiac disease[196] (Level 2+)

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

RR = relative risk

Table 23: Adjusted relative risk of first hospitalisation due to specific cardiac diseases[196] (Level 2+)

Hct (%)	34 to 36 (Ref)	37 to 39	≥40
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**
RR due to congestive heart failure, fluid overload or cardiomyopathy	1.00	0.85 (95% CI 0.77 to 0.95)	0.80 (95% CI 0.65 to 0.97)
RR due to ischemic heart disease, cerebrovascular disease or circulatory system disease	1.00	N/S	0.81 (95% CI 0.70 to 0.93)
RR due to other cardiac diseases	1.00	N/S	0.76 (95% CI 0.62 to 0.92)

RR = relative risk; NS = not significant

Table 24: Adjusted relative risk of first hospitalisation for patients with cardiac comorbid conditions (n=45,166)[196] (Level 2+)

Hct (%)	34 to 36	37 to 39	≥40
Hb (g/dl)	**11.3 to 12**	**12.3-13**	**≥13.3**
Relative risk	1.00	0.93	0.79
95% CI	N/A	0.89 to 0.98	0.71 to 0.87

Table 25: Adjusted relative risk of hospitalisation for patients with Hct 37 to 39% without pre-existing cardiac disease (3-year follow-up)[196] (Level 2+)

	RR	P value
All-cause hospitalisation	0.78	<0.0001
Any cardiac hospitalisation	0.74	0.0005

There were no new relevant studies identified in the rapid update review reporting the outcome hospitalisation. [2011]

Mortality

Nondialysis patients [2011]

Evidence statements:

There is moderate to high quality evidence[179,191,218] to show that:

- low Hb levels [<11 g/dL] compared to high Hb levels [>13 to ≤14 g/dL] are associated with an increased risk of mortality
- low Hb levels [≥11 to ≤12 g/dL] compared to high Hb levels [>13 to ≤14 g/dL] are associated with an increased risk of mortality
- low Hb levels [>12 g/dL] compared to high Hb levels [≥14 g/dL] are not associated with an increased risk of mortality.

There is uncertainty concerning all of the above results.

There is moderate quality evidence[179,191] to show that a decrement in Hb level of 1 g/dL is associated with an increased risk of mortality.

There is moderate quality evidence[374] to show:

- a decrement in Hb level of 1.5 g/dL is associated with an increased risk of mortality in patients with higher Hb levels [>14.5 g/dL] this decrement is associated with a decreased risk of mortality.

There is low quality evidence[187] to show that CHD-mortality is associated with lower Hb quintiles when GFR is estimated using the Cockcroft-Gault method. This effect is not evident when GFR is estimated using the MDRD method.

Evidence report:

Three studies[179,191,218,380] reported the risk for mortality associated with low and high haemoglobin levels. Risk of mortality was assessed over follow-up periods ranging from 16 months[218] to 27 months[191], while overall mortality rates ranged from 0.5% [191/27153][218] to 29% [245/853][179]. Mortality rates were stratified according to Hb ranges in one study[179] [<11 g/dL: 39.0% (68/174); 11.1 to 12 g/dL: 34.2% (74/216); 12.1 to 13 g/dL: 24.9% (50/201); >13 g/dL: 20.2% (53/262)].

An emerging trend suggests that lower Hb levels are associated with an increased risk of mortality compared with higher Hb levels. At higher Hb levels, a significant difference was not observed; however, there is some uncertainty concerning the precision of these effects (Figure 101 to Figure 103, Appendix CC).

Three studies reported the affect of incremental increases in Hb level on the risk of mortality. The overall mortality rates were: 20% [618/3028][191]; 29% [245/853][179]; 44.6% [748/1678][374].

In one study[191] an decrement of 10 g/L [1 g/dL] in Hb level was associated with a significantly increased risk of mortality in patients with: eGFR <15 mL/min [RR 0.91 (95% CI 0.84-0.99); eGFR of 15-29 mL/min [RR 0.86 (95% CI 0.81-0.92)]; eGFR of 30–59 mL/min [RR 0.81 (95% CI 0.71-0.92)] (Figure 104, Appendix CC).

An increment of 10 g/L [1 g/dL] in Hb level was also associated with a decreased risk in mortality in a second study[179] [HR 0.86 (95% CI 0.78-0.95)] (Figure 105, Appendix CC).

A third study[374] reported that an increment of 1.5 g/dL in Hb level was associated with a decreased risk in mortality [HR 0.86 (95% CI 0.79-0.94]. This benefit was increased in patients with Hb levels <14.5 g/dL [HR 0.70 (95% CI 0.63-0.78)]. However, in patients with Hb levels >14.5, an increment of

1.5 g/dL in Hb resulted in an increased risk of mortality [HR 1.31 (95% CI 1.09-1.56)] (Figure 106, Appendix CC).

A single study[187] reported the risk of CHD-related mortality for the lowest Hb quintiles [range: 7.6-14.6], as a continuous variable, compared with patients in higher Hb quintiles using different methods of estimating GFR. GFR estimated with the Cockcroft-Gault method reported an overall mortality rate of 11% [179/1639] and the proportion of patients who died within the groups were as follows: lower quintiles: 41% (74/179); other quintiles: 64% (115/179).

GFR estimated with the MDRD method reported an overall mortality rate of 9% [148/1639] and the proportion of patients who died within the groups were as follows: lower quintiles: 53/148; other quintiles: 95/148.

An increased risk in CHD-mortality associated with lower Hb quintiles was observed when GFR was estimated using the Cockcroft-Gault method (Figure 107, Appendix CC).

This study[187] also reported that there was no significant difference in CHD-related deaths in patients with the lowest quintiles of Hb and GFR compared with high Hb and GFR in subgroups for men and women; however, these subgroups included both CKD and non-CKD patients so the results are not presented here.

Haemodialysis patients

Data from a cohort (n=66,761) were stratified into increasing Hct levels and compared with an arbitrary Hct level of 33 to 35% over a 1-year follow-up period[70]:

Table 26: Adjusted relative risks (Level 2+)

Hct (%)	**<30**	**30 to 32**	**33 to 35 (Ref)**	**36 to 38**	**≥39**
Hb (g/dl)	**<10**	**10-10.7**	**11 to 11.7 (Ref)**	**12 to 12.7**	**≥13**
RR of all-cause mortality	1.74	1.25	1	NS	NS
RR of mortality from cardiac cause	1.57	1.25	1	NS	NS
RR mortality from infections	1.92	1.26	1	NS	NS

NS = not significant

In a 3-year follow-up study[196] participants (n=50,579) were stratified into Hct levels and compared with patients with the arbitrary reference of Hct 34 to 36% (n=22,192):

Table 27: Adjusted relative risk of mortality due to cardiac diseases[196]

Hct (%)	**34 to 36 (Ref)**	**37 to 39**	**≥40**
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**
Relative risk	1.00	0.92	0.83
95% CI	N/A	0.87 to 0.98	0.74 to 0.93

Table 28: Adjusted relative risk of all-cause mortality[196]

Hct (%)	**34 to 36 (Ref)**	**37 to 39**	**≥40**
Hb (g/dl)	**11.3 to 12 (Ref)**	**12.3-13**	**≥13.3**

Hct (%)	34 to 36 (Ref)	37 to 39	≥40
Relative risk	1.00	0.92	0.86
95% CI	N/A	0.88 to 0.96	0.80 to 0.93

Table 29: Adjusted relative risk of mortality for patients with Hct 37 to 39% without pre-existing cardiac disease[196]

	RR	P value
All-cause death	0.69	0.0002
Any cardiac death	0.69	0.0137

In one study[150] (n=309), 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**)

In a 4-year study[381], renal units with more than 87% of patients achieving target Hct ≥33% (Hb ≥11 g/dl) had a lower mortality rate than those with less than 64% of patients achieving target Hct (p<0.0001). A 10% point increase in the fraction of patients with Hct of more than or equal to 33% (Hb ≥11 g/dl) was found to be associated with a 1.5% decrease in mortality (p=0.003). (**Level 3**)

A retrospective cohort study with 1-year follow-up[204] (n=75,283) found an increase in the age group associated with higher all-cause and cause-specific mortality. Female patients had better outcomes. When compared with white patients, black patients and other ethnic minority patients had lower all-cause and cause-specific mortality. In the same study[204], mortality data were compared with Hct 30 to <33% (Hb 10 to <11 g/dl)[204], see Table 30.

Table 30: Adjusted relative risks[196] (Level 2+)

Hct (%)	<27 (n=9,130)	27 to 30 (n=22,217)	30 to <33 (Ref) (n=33,122)	33 to <36 (n=10,129)	1992 and 1993 data 33 to <36 (n=61,797)
Hb (g/dl)	**<9 g/dl (n=9,130)**	**9-<10 g/dl (n=22,217)**	**10 to 11 g/dl (Ref) (n=33,122)**	**11 to <12 g/dl (n=10,129)**	**1992 and 1993 data 11 to <12 g/dl (n=61,797)**
RR of all-cause death	1.33 95% CI 1.26-1.40	1.13 95% CI 1.08-1.17	1.00	NS	0.96 95% CI 0.92–0.99
RR of cardiac death	1.25 95% CI 1.15-1.35	1.11 95% CI 1.05-1.17	1.00	NS	Not reported
RR of infections death	1.53 95% CI 1.33-2.75	1.13 95% CI 1.02-1.26	1.00	NS	Not reported

NS = not significant

Kidney transplant patients [2011]

Evidence statement:

There is moderate quality evidence[380] showing there is no significant difference in the risk of mortality in kidney transplant patients with low Hb levels [≤10 g/dL] compared with high Hb levels [>10 to >13 g/dL] . There is some uncertainty in the result.

Evidence report:

One moderate quality study[380] examined the association between Hb level and mortality in kidney transplant patients.

Overall mortality rate over a median follow-up period of 8.2 years was 20% [251/825]. The proportion of patients who died within each Hb range was as follows: >10 to 11 g/dL: 31% (28/89); >11 to 12 g/dL: 27% (38/138); >12 to 13 g/dL: 30% (50/167); >13 g/dL: 30% (111/373); ≤10 g/dL : 41% (24/58).

There is uncertainty in the precision around the effect to determine whether Hb levels are associated with risk of mortality (Figure 108, Appendix CC).

MI, stroke and all-cause mortality

Predialysis patients

In one study[375] (n=2,333), the hazard ratio 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 or Hct <39% in men) when compared with those without anaemia (hazard ratio 1.51; 95% CI 1.27 to 1.81). (Level 3)

Nondialysis patients [2011]

Evidence statement:

There is moderate quality evidence[374] to show an increased risk in composite outcomes [MI, stroke, all-cause mortality] with a decrease in Hb of 1.5 g/dL; however, this effect was not observed in Hb levels >14.5 g/dL.

Evidence report:

Secondary analysis of two cohorts in one study[374] reported the risk associated with composite outcome (all-cause mortality, stroke, MI) for an increase in Hb of 1.5 g/dL: HR 0.89 (95% CI 0.82 to 0.96) and for an increase in Hb of 1.5 g/dL with Hb level less than 14.5 g/dL [HR 0.75 (95% CI 0.67 to 0.84). The risk increased with Hb levels greater than 14.5 g/dL [HR 1.22 (95% CI 1.03 to 1.45)] (Figure 109, Appendix CC).

Cardiac events - MI and CHD [2011]

Nondialysis patients

Evidence statement:

There is moderate quality evidence[374] to show no significant effect of a 1.5 g/dL decrease in Hb level and risk of cardiac events.

Evidence report:

Secondary analysis of two cohorts in one study[374] reported the risk associated with 1.5 g/dL increase in Hb and cardiac events. The results show that for every 1.5 g/dL increase in Hb there was no significant effect on cardiac events [HR 0.98 (95% CI 0.87 to 1.10)]. 22.5% patients [378/1678] experienced a cardiac event. The study also reported the risk associated with a 1.5 g/dL increase when the Hb level is less than 14.5 g/dL or greater than14.5 g/dL; there was no significant difference (Figure 110, Appendix CC).

Quality of life

Nondialysis patients [2011]

Evidence statement:

There is low quality evidence[127] showing a 10% reduction in haematocrit levels from baseline was associated with a significant decrease in the 'vitality' domain of the SF-36 health survey.

Evidence report:

One study[127] examined associations between haematocrit levels and changes in SF-36 score at 1 year. A 10% decrement in haematocrit levels from baseline was associated with a significantly decreased score for the 'vitality' domain of the SF-36 (change in score: 4.5 points; p=0.003). There were no significant changes in the scores in the remaining 7 domains.

Haemodialysis patients

When evaluated in epoetin-treated patients[226] (n=57) 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^2 0.57). (**Level 2+**)

Evidence statement [2011]:

There is moderate quality evidence[285] to show that a 1 g/dL increase in Hb level is associated with significantly higher QoL scores [SF-36 and CHEQ].

Evidence report [2011]:

A single study[285] assessed whether Hb concentration ≥11 g/dL at 6 months after initiation of haemodialysis was associated with better generic (SF-36) and disease-specific QoL [CHOICE Health Experience Questionnaire-CHEQ] at 1 year.

QoL scores at 1 year for patients who achieved haemoglobin concentrations of 11 g/dL at 6 months were significantly higher for the following SF-36 domains: physical functioning, role physical, bodily pain, role emotional, mental and social functions; and the following CHEQ domains: cognitive function and financial well-being. These patients also achieved a higher score for the following disease-specific domains: diet restriction and dialysis access. The effect size, ranged from 0.10 (general health) to 0.34 (mental health) in the SF-36 domains and from -0.07 (sexual function) to 0.31(finances) in the CHEQ domains.

A 1 g/dL increase in Hb (regardless of whether it fell to within 11 to 12 g/dL) was associated with significantly higher QoL scores for most of the generic and disease-specific QoL domains.

Effect of age on quality of life

Haemodialysis patients

In a subgroup analysis of epoetin-treated patients divided into age groups of more than or equal to 60 years (n=23) and less than 60 years (n=34), Hct levels were higher in the younger age group[226] ($p<0.05$). No differences were observed in improvements of quality of life scores using the Karnofsky scale or SIP score when these age groups were compared[226]. The same was true when patients were stratified into age groups of more than 60 years (n=34) and more than or equal to 65 years (n=15)[226]. (Level 2+)

Stroke [2011]

Nondialysis patients

Evidence statement:

There is moderate quality evidence[374] to show that a 1.5 g/dL decrease in Hb level is associated with an increased risk of stroke. This effect was observed in patients who had Hb levels <14.5 g/dL but not in those with Hb levels >14.5 g/dL.

Evidence report:

Secondary analysis of two cohorts in one study[374] reported the risk associated with a 1.5 g/dL increase in Hb and stroke. 13.9% patients [233/1678] experienced a stroke.

The results show that for a 1.5 g/dL increase in Hb there is a decreased risk of stroke [HR 0.85 (95% CI 0.73 to 0.99)]. This effect was observed for a 1.5 g/dL increase in the <14.5 group [HR 0.79 (95% CI 0.64 to 0.97)]. This effect was not seen in patients who had Hb>14.5 g/dL [1.02 (95% CI 0.71 to 1.46)] (Figure 111, Appendix CC).

Progression of CKD [2011]

Nondialysis patients

Evidence statement:

There is high quality evidence[179] to show that:

- lower time-averaged Hb levels [(<11 g/dL; 11.1 to 12 g/dL) compared to >13 g/dL] are associated with a significantly increased risk of progression to ESRD.
- a 10 g/L [1 g/dL] decrement in higher time-averaged Hb is associated with a significantly increased risk of progression to ESRD.

Evidence report:

One high-quality study[179] reported the risk associated with progression to end-stage renal disease (ESRD) for male nondialysis patients.

Overall rate of progression to ESRD was 23% [195/853]; the proportion of patients who progressed to ESRD for each Hb range was as follows: <11 g/dL: 40.2% (70/174); 11.1 to 12.0 g/dL: 30.0% (65/216); 12.1 to 13.0 g/dL: 17.9% (36/201); and >13 g/dL: 9.2% (24/262).

A lower time–averaged Hb (<11 g/dL; 11.1 to 12 g/dL) compared with >13 g/dL is associated with significantly higher risk of ESRD [<11 g/dL: HR 2.96 (95% CI 1.70 to 5.15); 11.1 to 12 g/dL: HR 1.81 (95% CI 1.07 to 3.06)]; however there is some uncertainty in the precision around the effects (Figure 112, Appendix CC).

The study also examined progression to ESRD associated with Hb level 12.1 to 13 g/dL compared with >13 g/dL and reported no significant difference was found; numerical data were not presented.

In addition, results showed that a 10 g/L [1 g/dL] higher time-averaged Hb is associated with a decreased risk of progression to ESRD [HR 0.74 (95% CI 0.65 to 0.84)] (Figure 113, Appendix CC).

4.1.5 Health economic methodological introduction [2011]

No economic studies were included in the 2006 guideline. A literature search was undertaken to identify papers published from September 2005 onwards.

One study[189] was identified that examined the association between haemoglobin level and cost in nondialysis patients with chronic kidney disease aged 65 years or older who were not receiving treatment for anaemia. This was a retrospective cohort analysis with multivariate regression (covariates: age, gender, GFR, diabetes, hypertension, liver cirrhosis, CAD, MI, LVH). Data was derived from a large US managed care database – this limits the applicability of the results to the guideline. Costs included inpatient and outpatient medical claims and pharmacy dispensing claims.

4.1.6 Health economic evidence statements [2011]

Evidence statement:

There is moderate quality evidence[189] that is partially applicable to the guideline to show that in untreated patients:

- low Hb [<11 g/dL] compared to higher Hb [>11 g/dL] is associated with increased costs.
- an decrement in Hb level of 1 g/dL is associated with increased cost.

Lefebvre and colleagues[189] reported that, in CKD patients untreated for anaemia, a haemoglobin level <11 g/dL was associated with an additional monthly cost of £320 (CI: £223, £408) compared to a haemoglobin level >11 g/dL. Every 1g/dL decrease in haemoglobin was associated with a £52 increase in cost (CI: £32-£71).

4.1.7 From evidence to recommendations

Data about the outcome of LVH were presented to the GDG[193]. Two studies which demonstrated an association between decreasing left ventricular mass and increasing haematocrit levels[143,287] were based on small sample sizes (n=9 and n=11) and the GDG weighed these studies accordingly in their deliberations.

Two studies were appraised that examined the rate of progression of renal failure but these were excluded as underpowered by the GDG[143,287] and hence, no evidence statements were presented for this outcome.

The GDG noted that the greater hospitalisation rate seen in a study based on registry data[70] could be a reflection of a sicker population and this may be another 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.

The study by Moreno et al[227] was excluded by the GDG because of a highly selected population (excluding both elderly and ill patients) and a lack of intention to treat analysis. The group agreed to increase the grade of one other study[196] from 3 to 2+ as the study participants had been subdivided according to Hct levels and a multivariate analysis of risk had been performed.

The GDG agreed that the evidence supported an association between decreased haematocrit and increased risk of hospitalisation.

The group felt that the evidence presented on mortality from one study[70] suggested that there was an increase in mortality between Hct <30 to <33% (Hb levels ~ 1 –11g/dl) when compared with 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[204,381] suggest that an 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 intercurrent illness. The issue was also raised that there might be a reverse causality and that patients requiring high amounts of epoetin may be sicker and hence more likely to require hospitalisation.

One study[150] concluded that the haematocrit level was not a predictor of survival and that other markers of morbidity were more important. The 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 men and women require different doses of ESA: women appear to need more ESA than men.

Only one study[222] 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).

Concerning quality of life in haemodialysis patients(n=57)[222], 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.

4.1.8 Recommendation and link to evidence [2011]

The current recommendations can be found at www.nice.org.uk/guidance/t205

4.1.8.1 Relative values of different outcomes

The GDG noted the outcomes that were important for decision making were mortality, quality of life, hospitalisation, cardiac events, stroke and composite events. There were no new relevant studies identified reporting the outcome LVH. Outcomes reporting change in LVMI and progression of CKD were not as influential in decision making. The GDG noted that the evidence was from observation cohort studies and the relationship between Hb levels and outcomes of interest may be influenced by other confounding factors such as chronic inflammation.

4.1.8.2 Trade off between clinical benefits and harms

The GDG noted:

- the overall trend of adverse outcomes at lower Hb levels in both non-dialysis and dialysis patients. There was limited evidence in the transplant population.
- the risk of mortality appears to increase below Hb 12 g/dL for the non-dialysis population and below 11 g/dL for the dialysis population, but there is a some heterogeneity in the data.
- There was no new relevant studies identified considering children.

- more evidence is available at the 2011 update for the non-dialysis population than was available at the time of the original guideline.

The GDG also debated if there were other subgroups where different relationships between Hb levels and outcomes could be distinguished, for example sex, ethnicity or people with diabetes. However there is insufficient evidence on which to base different recommendations for these sub-groups.

4.1.8.3 Economic considerations

No cost effectiveness analyses were identified that compared initiating management of anaemia at different threshold Hb levels.

One cohort study was identified that examined the association between cost and Hb level in untreated people with CKD and reported that lower Hb was associated with higher costs in patients not treated for anaemia.

4.1.8.4 Quality of evidence

There was low to moderate quality evidence from prospective and retrospective cohort studies. The majority of the studies were adjusted for confounding factors but the GDG considered that confounding (for example the more severe the chronic kidney disease, the lower the Hb is likely to be) remained an important issue in deciding at which level of Hb to initiate management.

4.1.8.5 Other considerations

The GDG noted that the Hb level at which patients are at increased risk for mortality differed between non-dialysis and dialysis patients, however there was some heterogeneity in the results. The GDG debated whether to make separate recommendations for the different population groups but the level of uncertainty and the strength of the evidence did not allow firm conclusions to be drawn.

The GDG noted the complexity in deciding the level of Hb at which to start treatment, also noting that different patients become symptomatic at different levels of Hb concentration.

The GDG considered the recommendation drafted in the original guidance together with the additional evidence accruing since publication of the original guidance. The GDG unanimously agreed that the recommendation to initiate management of anaemia in people with CKD and Hb levels below 11 g/dl did not require change. The GDG's rationale for having the intervention point within the aspirational target range and not at the lower limit of the range is because investigation and management would begin before the Hb level had fallen below the lower limit of the aspirational range (see paragraph 6.9), thereby allowing time for management to maintain Hb levels within the range rather than having to raise them to within the range.

However, the GDG felt that the recommendation should be amended to read 'fallen below 11 g/dl' (original: 'less than or equal to 11 g/dl') to highlight that management and investigation was indicated when Hb levels were declining and not when they were stable.

The GDG also felt that they should recommend investigation and management of anaemia in individual patients who are thought to be symptomatic from anaemia despite higher levels of Hb or below the normal range for people with CKD, for example between 11 and 12 g/dL. The recommendation was modified to reflect this.

The 2011 update to the guidance on anaemia in CKD (CG114) indicated that the blood count should be monitored in CKD, without specifying the interval. The GDG for the 2015 update felt that blood

count monitoring has to be tailored to the patient, and usually coincides with eGFR testing (to avoid unnecessary needlesticks).

4.2 Diagnostic role of glomerular filtration rate

This section was updated and replaced in 2021. See www.nice.org.uk/guidance/ng203/evidence for the 2021 evidence reviews.

4.3 Diagnostic tests for the prediction of response to iron therapy [2015]

4.3.1 Introduction

Anaemia of CKD is contributed to by the development of iron-restricted erythropoiesis. This is from increased blood loss from haemodialysis and blood testing, reduced iron absorption from raised hepcidin levels and from functional iron deficiency (FID). FID is a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores, as characterised by the use of the serum ferritin (SF) test, which in FID is normal or raised. It was originally described to explain why iron restriction became evident with the use of erythropoietic agents. Lack of iron is reflected in reduced synthesis or availability of haem, and will thus, contribute to the development of anaemia. The reduced absorption of iron across the gut in the face of high hepcidin levels (known to be associated with CKD) can be at least overcome to some extent by providing bone marrow macrophages with iron by administering it intravenously to patients with CKD.

There is good understanding that haemoglobin (Hb) concentrations alone (in g/litre) do not give adequate information about the aetiology of anaemia or potential for treatments available to ameliorate the anaemia. Given the vital importance of iron for Hb synthesis, tests must provide some understanding of iron homeostasis within the patient. Traditional tests of iron fall short, since low levels of SF are unusual in CKD, yet we know that there is iron-restricted erythropoiesis, because patients respond to intravenous iron with normal or even raised ferritin levels. If there are indications that the patient has an inflammatory process, such as a raised C Reactive Protein or plasma viscosity, there is a much higher likelihood that both ferritin and hepcidin levels will be increased. The aetiology of raised SF in this setting is just a function of increased storage cell 'leakage'.

Another way of detecting iron deficiency is to look at the red blood cell Hb content, either in reticulocytes or in the entire circulating red cell population. Hypochromic erythropoiesis is the end result of reduced iron availability. Looking at the mean corpuscular Hb will show if iron restriction is present, but changes to this value may take time to develop. It is possible though to look for the percentage of hypochromic red cells (%HRC), or look to the reticulocytes for their Hb content (CHr or Ret-He). Reticulocytes are present in the circulation for 4-5 days, so give a discrete population to study. Reduced red cell Hb can be reflective of reduced haem availability or globin. Therefore, the red cell analyte values (%HRC, CHr, Ret-He) may be affected by the presence of haemoglobinopathies. Similarly, it is important to be mindful to exclude causes other than functional iron deficiency for the cause of anaemia in CKD, such as serum B12, folate deficiency, or hypoplastic or dysplastic marrow disorders, such as red cell aplasia or myelodysplasia.

Crucially the most important criterion for evaluating a test for iron deficiency is how well it predicts which patients will respond to the administration of intravenous iron. It is important to recognise that each test in isolation cannot, with complete certainty, indicate that the individual patient will respond to intravenous iron.

A significant majority of UK laboratory analysers are potentially able to assay the red cell analytes of %HRC, CHr and Ret-He using different technologies. Other available analysers can also access red cell analytes reflective of iron homeostasis as a research parameter presently. This chapter explores the clinical utility of the various iron-related analytes in the context of anaemia of CKD.

The GDG wished to assess the clinical utility of tests of storage iron (ferritin), serum transport of iron (transferrin saturation [TSAT]), and haem content within the red blood cells (%HRC, CHr, Ret-He). The GDG were aware that serum hepcidin assays are carried out in research settings, but noted that the evidence to date suggested that this assay does not provide sufficient clinical utility for predicting response to intravenous iron.

The GDG wished to understand which of these tests were most accurate at predicting response to iron therapy. However, it was also acknowledged that evaluating response to iron therapy is not independent of first assessment of iron status and the same tests need to be viewed in continuum throughout diagnosis, monitoring and maintenance.

4.3.1.1 Review question (clinical effectiveness of diagnostic tests): In people with suspected (or under investigation for) anaemia in chronic kidney disease, what is the comparative clinical and cost effectiveness of the following tests or combination of tests at predicting response to iron, when each is followed by the appropriate treatment in order to improve patient outcomes?

- Iron (Fe), total iron binding capacity (TIBC), and TSAT (calculated by serum Fe levels divided by TIBC)
- Ferritin
- Soluble transferrin receptor (sTfR)
- % hypochromic red cells (HRC)
- Reticulocyte haemoglobin content (CHr)

Table 31: PICO characteristics of question for clinical effectiveness of diagnostic tests review

Population	Adults, young people and children suspected (or under investigation for) anaemia in chronic kidney disease
Index diagnostic test + treatment	Any of the tests or combination of tests listed below followed by iron therapy treatment: • Ferritin and TSAT (iron [calculated by serum iron levels divided by TIBC]) • Ferritin and CHr • Ferritin and sTfR • Ferritin and %HRC • %HRC alone • CHr alone • TSAT alone • sTfR
Comparator diagnostic tests + treatment	Any of the tests or combination of tests listed above followed by iron therapy treatment Exclusions: Studies where patients are given different treatments following the tests will be excluded.
Outcomes	• ESA use to maintain target Hb • Number of patients responding to iron therapy • Quality of life
Study design	Diagnostic RCTs

This review was combined with the diagnostic accuracy review and the evidence is reported together in Section 4.3.2

4.3.1.2 Review question (diagnostic accuracy): What is the accuracy of the following tests, or combination of tests, at predicting response to iron therapy in patients with CKD?

- Iron (Fe), total iron binding capacity (TIBC), and TSAT (calculated by serum Fe levels divided by TIBC)
- Ferritin
- Soluble transferrin receptor (sTfR)
- % hypochromic red cells (HRC)
- Reticulocyte haemoglobin content (CHr)

For full details see review protocols in Appendix C.

Table 32: PICO characteristics of question for diagnostic accuracy review

Population	Adults, young people and children suspected (or under investigation for) anaemia of CKD
Index tests	• Ferritin and TSAT (iron [calculated by serum iron levels divided by TIBC]) • Ferritin and CHr • Ferritin and sTfR • Ferritin and %HRC • %HRC alone • CHr alone • TSAT alone • sTfR
Reference standard	Any erythropoietic response as prospectively defined by study, for example, Hb response of >10 g/litre. **Note:** Evidence from papers using similar erythropoietic response as reference standard will be considered together, for example, Hb response of ≥15% and Hct absolute increase of 5%
Outcomes	• Sensitivity • Specificity • Positive predictive values • Negative predictive values. • AUC
Study design	Diagnostic accuracy cohort studies

Table 33: Definitions of diagnostic tests for iron deficiency anaemia

Test	Definition
Serum ferritin (SF)	A measure of iron stores found in the blood; affected by other factors – low in iron deficiency
Serum iron	Circulating iron – low in iron deficiency
Serum total iron binding capacity (TIBC)	The amount of circulating protein able to bind iron; this protein is transferrin – high in iron deficiency
Transferrin saturation (TSAT)	The percentage of transferrin binding sites occupied by iron – low in iron deficiency
Reticulocyte haemoglobin content (CHr)	A measure of the amount of iron available in the bone marrow when the new red blood cells were made (red blood cells that are a few days old).
Percentage of hypochromic red blood cells (%HRC)	In iron deficiency, more cells have low Hb content and are hypochromic; this is the percentage of all red cells that are hypochromic. Full blood count

Test	Definition
	(FBC) specimens should be processed quickly (within 6 hours) to avoid red cell swelling which can give a false positive result.
Serum/Soluble transferrin receptor (sTfR)	A receptor that is expressed on the membrane of red blood cells. The receptors can come off the blood cells and be detected in the serum. If patients are iron deficient they express more transferrin receptors on the red cells.

Table 34: Threshold considered for each index test in this review

Index test	Thresholds
TSAT	<20%
SF	<100 micrograms/litre
CHr	<29 pg according to American NKF/DOQI guidelines or <32.2 pg according to guidelines on treatment of Renal Anaemia published by the Japanese society for dialysis therapy
%HRC	>6% (based on Tessitore 2001)
sTfR	Unclear

Table 35: Definitions of summary measures for diagnostic accuracy studies

Measure	Definition
True positives (TP)	Correct positive test result – number of people diagnosed with iron-deficiency anaemia with a positive index test result.
True negatives (TN)	Correct negative test result – number of people diagnosed as not having iron-deficiency anaemia with a negative index test result.
False positives (FP)	Incorrect positive test result – number of people diagnosed as not having iron-deficiency anaemia with a positive index test result.
False negatives (FN)	Incorrect negative test result – number of people diagnosed with iron-deficiency anaemia with a negative index test result.
Sensitivity (%)	**Proportion** of those **with** iron-deficiency anaemia (based on a reference standard) who are **positive** on the index test.
Specificity (%)	**Proportion** of those **without** iron-deficiency anaemia (based on a reference standard) who are **negative** on the index test.
Positive predictive values (PPV)	**Probability** of having iron-deficiency anaemia in a patient with a positive index test result
Negative predictive values (NPV)	**Probability** of not having iron-deficiency anaemia in a patient with a negative index test result
Positive likelihood ratio (PLR)	How many times more likely a **positive** test result occurs in patients with compared with those without iron-deficiency anaemia.
Negative likelihood ratio (NLR)	How many times more likely a **negative** test result occurs in patients with compared with those without iron-deficiency anaemia.
Area under the curve (AUC)	Overall summary of performance or diagnostic accuracy of an index test (compared against a reference standard)

4.3.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of a variety of diagnostic tests at predicting response to iron therapy. As well as RCTs, we also searched for cohort studies exploring

the diagnostic accuracy of the various tests (DTA studies) compared with reference standards of either bone marrow aspiration or post-iron therapy erythropoietic response. The tests investigated are described in Table 33.

Eleven studies were included in the review[12,51,54,63,93,109-111,166,332,350], and these are summarised in Table 36. The type of study (RCT/DTA) has also been indicated. As noted below, the studies involved haemodialysis (9 studies), peritoneal dialysis (1 study) and non-dialysis CKD patients (1 study).

See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix L, GRADE tables in Appendix K and excluded studies list in Appendix M.

Of the included studies, two are diagnostic RCT studies[111,166] comparing CHr with either TSAT alone, or TSAT and SF combinations. The other nine studies included papers are diagnostic accuracy studies. In three of the studies, authors supplied enough information for us to construct 2x2 tables of true positives, false positives, true negatives and false negatives in order to calculate the sensitivity, specificity, positive and negative predictive values for the various tests compared with the reference standard of post-iron therapy haematologic response [63,109,332]. For five of the papers, the raw data (true positives and negatives, false positives and negatives) was calculated using the author supplied sensitivities, specificities and number of patients classified as 'responders'[12,51,93,110,350]. These eight papers investigated all the tests in our protocol, although, only one reported on sTfR. We have included one additional study[54] where authors reported sensitivity and specificity, or the AUC from the receiver operator characteristic (ROC) plot, but have not supplied enough (or any) raw data to allow calculation of 2x2 tables to verify their reported accuracy ratings. The GRADE ratings for these papers (see Appendix K) reflect the omission of this valuable raw data.

Table 36: Summary of studies included in the review

Study	Population	Index test(s)	Reference standard	Prior intravenous iron therapy	Comments
Ahluwalia 1997[12] DTA study	Haemodialysis patients	sTfR	Hb increase	No iron dextran in previous 6 months	Outcomes reported: author-reported sensitivity and specificity=2x2 data calculated Note: treatment consisted of oral iron and no EPO, 3 month duration.
Bovy 2007[51] DTA study	Haemodialysis patients	• CHr • %HRC • TSAT • SF	Hb increase	Unclear	Outcomes reported: author-reported sensitivity and specificity=2x2 data calculated, AUC Note: treatment consisted of low-dose high-frequency IV iron, stable (unchanged) EPO, 4 week duration.
Buttarello 2010[54] DTA study	Haemodialysis patients	sTfR	Hb increase	3 week iron wash out prior to the study	Outcomes reported: author-reported sensitivity and specificity, AUC
Chen 2006[63]	Haemodialysis	TSAT and/or	Hct increase or rHuEPO	No iron supplementation in the	Outcomes reported: diagnostic accuracy raw

Study	Population	Index test(s)	Reference standard	Prior intravenous iron therapy	Comments
DTA study	patients	SF	decrease	preceding 3 months	data Note: 'and/or' nature of index test with no indication of how many single SF, single TSAT or combination SF + TSAT used. Treatment consisted of low-dose high-frequency IV iron, EPO reactive to maintain target Hct, 5 month duration.
Domrongkichaiporn 1999[93] DTA study	Peritoneal dialysis patients	• CHr • TSAT • SF	Hb increase	Receiving oral iron supplementation but no IV iron therapy within one month of study	Outcomes reported: author-reported sensitivity and specificity = 2x2 data calculated. Note: population different from majority of included evidence. Treatment consisted of high-dose low-frequency IV iron, 'constant' EPO, 3 month duration.
Fishbane 1996[110] DTA study	Haemodialysis patients	• TSAT • SF	Hct increase or rHuEPO decrease	Possibly as history of intolerance to IV iron dextran was an exclusion criteria	Outcomes reported: author-reported sensitivity and specificity=2x2 data calculated. Note: treatment consisted of low-dose high-frequency IV iron, EPO reactive to maintain target Hct, 2 month duration.
Fishbane 1997[109] DTA study	Haemodialysis patients	• CHr • %HRC • TSAT • SF	Corrected reticulocyte index increase	No IV iron treatment in the previous four weeks.	Outcomes reported: diagnostic accuracy raw data. Note: treatment consisted of high-dose low-frequency IV iron, on EPO, 2 week duration.
Fishbane 2001[111] RCT	Haemodialysis patients	• CHr • TSAT or SF	N/A – RCT comparison of tests	No IV iron in the previous month	Outcomes reported: rHuEPO use Note: treatment consisted of low-dose high-frequency IV iron, EPO reactive to maintain target Hct, 6 month duration. No quality of life or patient

Study	Population	Index test(s)	Reference standard	Prior intravenous iron therapy	Comments
					outcomes reported.
Kaneko 2003[166] RCT	Haemodialysis patients	• CHr • TSAT	N/A – RCT comparison of tests	Unclear	Outcomes reported: rHuEPO use Note: CHr threshold higher than pre-defined for this review. Treatment consisted of low-dose high-frequency IV iron, EPO reactive to maintain target Hct, 16 weeks duration. No quality of life or patient outcomes reported.
Stancu 2010A[332] DTA study	Non-dialysis patients	• TSAT • SF • TSAT and SF	Hb increase	No previous IV iron	Outcomes reported: diagnostic accuracy raw data, AUC Note: population different from majority of included evidence. Treatment consisted of high-dose low-frequency IV iron, and no EPO information, for a 3 month duration.
Tessitore 2001[350] DTA study	Haemodialysis patients	• CHr • %HRC • TSAT • SF	Hb increase	Unclear	Outcomes reported: author-reported sensitivity and specificity=2x2 data calculated, AUC Note: treatment consisted of low-dose high-frequency IV iron, 'constant' EPO, 6-19 weeks duration.

4.3.2.1 Methodology of review-data synthesis

Results from the diagnostic test and treat RCTs comparing CHr with either TSAT alone, or TSAT or SF combinations are reported separately to the results from the diagnostic accuracy studies (see Table 37, also see forest plots in Appendix L)

Evidence from the diagnostic test accuracy studies is presented as ROCS curves and forest plots of sensitivity and specificity with their 95% confidence intervals presented side-by-side for individual studies using Cochrane Review Manager (RevMan5) software. Area under the curve information is listed when supplied by authors, the rule of thumb for AUC is as follows: 0.50-0.60 very poor; 0.60-0.70 poor; 0.70-0.80 moderate; 0.80-0.90 good; 0.90-1.00 excellent.

When data from 5 or more studies was available, a diagnostic meta-analysis was carried out. This was true for two tests, TSAT and SF. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one receiver operating characteristics (ROC) curve in Microsoft EXCEL software (for forest plots please see Appendix L). Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a

random effects approach (in WinBUGS® software - for the program code see Appendix P). This model also assesses the variability by incorporating the precision by which sensitivity and specificity have been measured in each study. From the WinBUGS® output we report the summary estimate of sensitivity and specificity (plus their 95% confidence intervals) as well as between study variation measured as logit sensitivity and specificity as well as correlations between the two measures of variation. The summary diagnostic odds ratio with its 95% confidence interval is also reported.

A summary ROC curve comparing all tests is also presented (see forest plots in Appendix L).

Quality of evidence

Risk of bias for each outcome was determined by the QUADAS-2 criteria (Table 78 in Appendix J). This informed the risk of bias rating given on the GRADE tables (Appendix K). The QUADAS-2 covers four domains: patient selection, the index test, the reference standard and flow and timing. Each domain is assessed for risk of bias, and the first three are also assessed for applicability (in reference to the review protocol). If there were two or more major limitations according to the QUADAS criteria, a rating of very serious limitations was given. If there was a single major limitation a rating of serious limitations was given. Evidence from the included studies is summarised in the clinical evidence summary (Table 37).

Table 37: Clinical evidence summary: Diagnostic RCTs

Test comparison	Number of studies	Imprecision	GRADE rating	Absolute difference	Moderate control event rate (per 1000)	Mean control group value for continuous outcomes
rHuEPO use following treatment based on:						
CHr compared to TSAT Kaneko 2003	1 (n=183)	Serious imprecision	LOW	MD 1066 higher (201.46 to 1930.54 higher)		2469 U/week
CHr compared to TSAT+SF Fishbane 2001	1 (n=138)	No serious imprecision	MODERATE	MD 823 lower (4831.77 lower to 3185.77 higher)		11772 U/week

Table 38: Clinical evidence summary: Diagnostic accuracy cohort studies

Test	Sensitivity	Specificity	AUC	Risk of bias and applicability
CHr	4 cohort studies (pre-defined threshold n=178) Bovy 2007: 33% Domrongkitchaiporn 1999: 47% Tessitore 2001:56% (lower threshold n = 32) Fishbane 1997: 100%	4 cohort studies (pre-defined threshold n=178) Bovy 2007: 100% Domrongkitchaiporn 1999: 83% Tessitore 2001:93% (lower threshold n = 32) Fishbane 1997: 80%	3 cohort studies (n=226) Bovy 2007: 0.75 Buttarello 2010: 0.74 Tessitore 2001: 0.80	Serious risk of bias (based on patient selection limitations in the diagnostic cohorts)
%HRC	3 cohort studies (pre-defined threshold =157) Bovy 2007: 92% Tessitore 2001:82% (higher threshold n = 32) Fishbane 1997: 43%	3 cohort studies (pre-defined threshold =157) Bovy 2007: 75% Tessitore 2001:95% (higher threshold n = 32) Fishbane 1997: 80%	3 cohort studies (n=226) Bovy 2007: 0.94 Buttarello 2010: 0.72 Tessitore 2001: 0.93	Serious risk of bias (based on patient selection limitations in the diagnostic cohorts)
sTfR	1 cohort study (n=17) Ahluwalia 1997: 88%	1 cohort study (n= 17) Ahluwalia 1997: 78%	2 cohort studies (n=157) Bovy 2007: 0.99	Very serious risk of bias (based on patient selection

Test	Sensitivity	Specificity	AUC	Risk of bias and applicability
			Tessitore 2001: 0.78	limitations and flow and timing of index and reference test)
TSAT	6 cohort studies (n=357) Pooled MA: 61% Bovy 2007: 91% Domrongkitchaiporn 1999: 20% Fishbane 1996: 81% Fishbane 1997: 57% Stancu 2010A: 50% Tessitore 2001: 59%	6 cohort studies (n=357) Pooled MA: 79% Bovy 2007: 71% Domrongkitchaiporn 1999: 100% Fishbane 1996: 63% Fishbane 1997: 80% Stancu 2010A: 83% Tessitore 2001: 78%	4 cohort studies (n=326) Bovy 2007: 0.90 Buttarello 2010: 0.56 Stancu 2010A: 0.73 Tessitore 2001: 0.76	Serious risk of bias (based on patient selection limitations in the diagnostic cohorts)
SF	6 cohort studies (n=357) Pooled MA: 39% Bovy 2007: 27% Domrongkitchaiporn 1999: 13% Fishbane 1996: 48% Fishbane 1997: 71% Stancu 2010A: 48% Tessitore 2001: 35%	6 cohort studies (n=357) Pooled MA: 81% Bovy 2007: 100% Domrongkitchaiporn 1999: 100% Fishbane 1996: 75% Fishbane 1997: 60% Stancu 2010A: 85% Tessitore 2001: 78%	3 cohort studies (n=294) Buttarello 2010: 0.53 Stancu 2010A: 0.71 Tessitore 2001: 0.63	Serious risk of bias (based on patient selection limitations in the diagnostic cohorts)
TSAT and/or SF	2 cohort studies (n=200) Chen 2006: 27% (and/or) Stancu 2010A: 33% (and)	2 cohort studies (n=200) Chen 2006: 92% (and/or) Stancu 2010A: 98% (and)	1 cohort study (n=100) Stancu 2010A: 0.59 (and)	No serious limitations

4.3.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

New cost-effectiveness analysis

A cost-utility analysis of different iron deficiency test and treat strategies was conducted from a UK NHS and personal social services perspective with health outcomes expressed as quality adjusted life years (QALYs). Full details of the analysis can be found in Appendix O. The following test and treat strategies were included in the model:

Table 39: Test and treat strategies

Rule for initiating corrective iron therapy	Haemodialysis patients – test protocol	Non-haemodialysis patients – test protocol
TSAT <20%	Full blood count (FBC) monthly to measure Hb SF 3-monthly to diagnose iron overload TSAT monthly to diagnose iron deficiency	FBC 3-monthly to measure Hb SF 3-monthly in patients receiving iron therapy to diagnose iron overload TSAT 3-monthly to diagnose iron deficiency
SF <100 micrograms/litre	FBC monthly to measure Hb SF monthly to diagnose iron deficiency	FBC 3-monthly to measure Hb SF 3-monthly to diagnose iron deficiency
SF <200 micrograms/litre	FBC monthly to measure Hb SF monthly to diagnose iron deficiency	FBC 3-monthly to measure Hb SF 3-monthly to diagnose iron deficiency
CHr <29 pg	FBC+CHr monthly to measure Hb and diagnose iron deficiency SF 3-monthly to diagnose iron overload	FBC+CHr 3-monthly to measure Hb and diagnose iron deficiency SF 3-monthlyin patients receiving iron to diagnose iron overload
HRC >6%	FBC (including %HRC) monthly to measure Hb and diagnose iron deficiency SF 3-monthly to diagnose iron overload	FBC (including %HRC) 3-monthly to measure Hb and diagnose iron deficiency SF 3-monthlyin patients receiving iron to diagnose iron overload
TSAT <20% and/or SF <100 micrograms/litre	FBC monthly to measure Hb TSAT and SF monthly to diagnose iron deficiency	FBC 3-monthly to measure Hb TSAT and SF 3-monthly to diagnose iron deficiency
TSAT <20% and SF <100 micrograms/litre	FBC monthly to measure Hb TSAT and SF monthly to diagnose iron deficiency	FBC 3-monthly to measure Hb TSAT and SF 3-monthly to diagnose iron deficiency

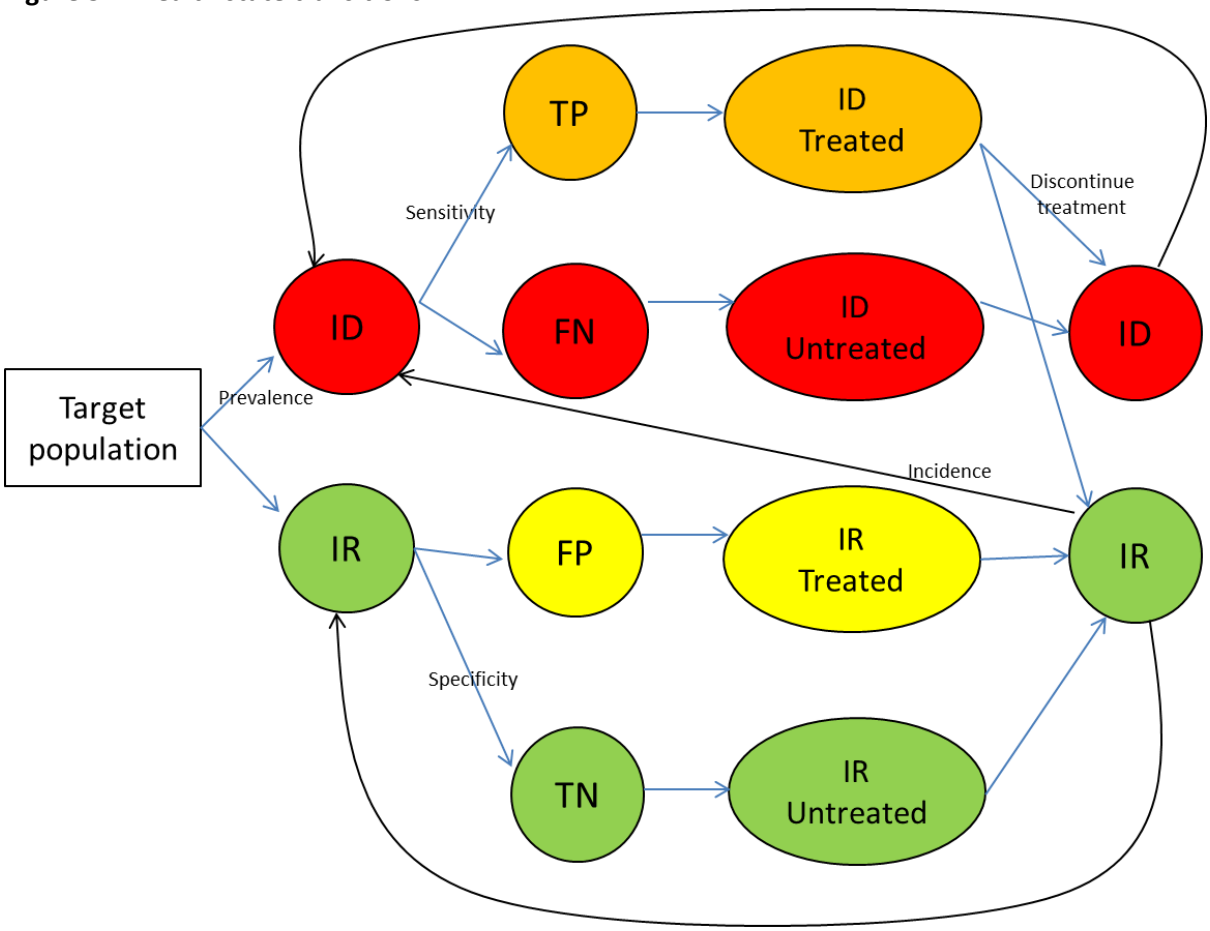
In the model, adults with suspected (or under investigation for) iron deficiency anaemia in chronic kidney disease were split into two subgroups:

- Haemodialysis patients (receiving dialysis in-hospital)
- Pre-dialysis and peritoneal dialysis patients

The time horizon of the model was 12 months, which is long enough to capture the difference in costs and effects from re-testing: assumed to be every month for haemodialysis patients and for other patients every 3 months.

A state transition (Markov) model was constructed to calculate the costs and QALYs associated with each test; the key health states and transitions can be seen in Figure 5.

Figure 5: Health state transitions



IR=iron replete, ID=iron deficient, FN=false negative, FP=false positive, TN=true negative, TP=true positive.

All individuals in the model are tested to predict whether their Hb would respond to iron therapy. People who are found to have iron deficiency according to the test cut-off are given a correction dose of iron therapy, and the others are not given corrective iron therapy. Corrective iron therapy would stop after a month. It was assumed that all patients would be re-tested, and each time they would receive a correction dose of iron therapy only if indicated by the test result. Haemodialysis patients were assumed to have a maintenance dose of iron in months when they were not receiving a correction dose.

Data sources

Full details of the model data and assumptions can be found in Appendix O. In summary:

- Test accuracy was taken from the systematic review of diagnostic studies (Section 4.3.2). These are summarised in Table 33.
- The prevalence of iron deficiency (proportion whose Hb will respond to iron therapy) was pooled from the studies in the systematic review of diagnostic studies (Section 4.3.2)

- The incidence of new iron deficiency determines how long the benefit of iron therapy is sustained. In the absence of evidence this was assumed to be 10% per month in the base case and up to 20% in sensitivity analyses
- Quality of life data (SF-36) for 2 cohorts, Hb less than 11 (n=229) and Hb 11-12 (n=223), were taken from a USA study of anaemia in CKD patients[106]. This data was then converted to EQ-5D using the equation by Ara and Brazier[22] and then used to calculate QALYs.
- Test costs were the median costs from a small sample of NHS Trusts. These are summarised in Table 40.
- We averaged the cost of a number of different iron therapy regimens. BNF list prices were used for the drug cost. The cost of administrator time, transport, consumables all vary according to the number of infusions. The cost of clinic space and nurse time also varied according to the duration of infusion and hence the throughput achievable. Unit costs were taken from a cohort of 365 patients at a London hospital[378] – **Error! Reference source not found.**.
- We used the Onken study [260] from the guideline systematic review (6.15) to estimate the risk of a treatment-related serious adverse event (SAE) with IV. For each of these events we attributed a treatment cost from the NHS reference costs database[91].
  - In a sensitivity analysis we incorporated the effects of fatal adverse events: 1.4% (see Table 41) of SAEs which we derived from the EMA report on the risks of IV iron therapy[102] and an assumed QALY loss of 20 per death. This is very conservative since there is no evidence that iron therapy increases mortality overall, and indeed, it might reduce mortality.
- We conservatively used the highest treatment discontinuation rate from the review[209] and assumed that everyone discontinuing treatment would remain iron deficient until the next routine test (Chapter 6.15).
- Two studies[195,323] in the guideline systematic review (Chapter 6.15) estimated the difference in ESA dose attributable to iron therapy.

Table 40: Test accuracy

Test strategy	Sensitivity	Specificity	Source	Median cost (£)
TSAT <20%	61%	79%	Diagnostic meta-analysis – see 4.3.2	6.18
SF <100 micrograms/litre	39%	81%	Diagnostic meta-analysis – see 4.3.2	5.11
SF <200 micrograms/litre	77%	38%	Fishbane1996[110]	5.11
CHr <29 pg	57%	93%	Tessitore2001[350]	4.71
%HRC >6%	82%	95%	Tessitore2001[350]	3.04
TSAT <20% and/or SF <100 micrograms/litre	76%	64%	From diagnostic meta-analyses, assuming tests are independent	
TSAT <20% and SF <100 micrograms/litre	33%	98%	Stancu2010[332]	

Table 41: Fatal events as a proportion of serious adverse events (SAEs) after IV iron therapy (post-marketing data from European Medicines Agency report)

	Fatal SAEs (a)	SAEs (b)	% (=a/b)
Iron dextran	8	366	2.2%
Iron gluconate	6	546	1.1%
Ferric carboxymaltose	1	178	0.6%
	15	**1090**	**1.4%**

Note: The data in the EMA report was presented in different ways with different denominators. It was not possible to extract the data in this format for other iron preparations, such as iron sucrose. Iron gluconate is not available for intravenous administration in the UK.

Results

The results of the base case analysis are presented in Table 42. For haemodialysis patients, %HRC more than 6 dominated all other strategies (it led both to more QALYs and lower cost). For the other patients, TSAT less than 20% and SF less than 100 micrograms/litre was the lowest cost strategy, but %HRC was the most cost-effective, costing £11,300 per additional QALY gained. The results were subjected to a number of sensitivity analyses. %HRC was ranked 1st in all but the following scenarios:

- When we used the accuracy data from Bovy2007 instead of Tessitore2001 for %HRC (optimal strategy = CHr less than 29 pg – both subgroups).
- When we assumed 1.4% of SAEs were fatal (based on EMA data) and no survival benefit from achieving target Hb (optimal strategy = TSAT less than 20% and SF less than 100 micrograms/litre for both subgroups).
- When we used the cost of a day case from the NHS reference costs for each iron infusion for non-haemodialysis patients (optimal strategy = TSAT less than 20% and SF less than 100 micrograms/litre)

Table 42: Base case results (probabilistic) - cost-effectiveness

Pre-dialysis/ peridialysis	Mean costs				Mean QALYs	Net monetary benefit				
Strategy	Tests	Iron	Side effects	Total (a)	(b)	=20000b-a	Rank (95% CI)			P(c/e)
Non-haemodialysis patients										
TSAT <20%	44	237	73	355	0.7893	15430	5	3	5	0.0%
SF <100 micrograms/litre	32	182	56	271	0.7853	15436	4	3	6	0.1%
SF <200 micrograms/litre	32	430	132	594	0.7912	15230	7	6	7	0.0%
CHr <29 pg	24	171	52	247	0.7880	15513	2	1	3	7.1%
%HRC >6%	19	203	63	284	0.7918	15551	1	1	3	88.7%
TSAT <20% and/or SF <100 micrograms/litre	57	324	100	481	0.7915	15350	6	4	7	0.0%
TSAT <20% and SF <100 micrograms/litre	57	95	29	181	0.7826	15471	3	1	6	4.0%
Haemodialysis patients										
TSAT <20%	131	518	245	893	0.7919	14946	5	3	5	0.0%
SF <100 micrograms/litre	97	495	209	802	0.7897	14993	4	3	5	0.0%
SF <200 micrograms/litre	97	721	567	1386	0.7875	14364	7	6	7	0.0%
CHr <29 pg	77	451	139	668	0.7927	15185	2	1	3	9.4%
%HRC >6%	57	453	142	652	0.7950	15249	1	1	2	89.5%
TSAT <20% and/or SF <100 micrograms/litre	172	594	365	1130	0.7912	14693	6	5	7	0.0%
TSAT <20% and SF <100 micrograms/litre	172	412	77	661	0.7873	15085	3	2	6	1.0%

Note: P(c/e), probability that the strategy is the most cost-effective. This is calculated as the number of simulations in which that strategy had the highest net monetary benefit (NMB). Rank is the rank of the strategy in term of its NMB (1=highest NMB, 7=lowest NMB).

4.3.4 Evidence statements

Clinical

CHr

Two studies were identified looking at the performance of CHr to predict response to iron therapy based on average dose of ESA used to maintain target haematocrit. Moderate quality evidence from one RCT[111] (n=138) favoured using CHr at a threshold of less than 29 pg compared with using TSAT or SF. Low quality evidence from another RCT[166] (n=183) favoured the use of TSAT alone compared with using CHr at a higher threshold of less than 32.5 pg.

Low quality evidence based on raw data scores in three cohort studies[51,93,350] (n=178) using a less than 29-30 pg threshold showed highly variable and mediocre sensitivity (point estimates of 33%, 47% and 57% with a range of 10-73%) and high but variable specificity (point estimates of 100%, 83% and 93% with a range of 36-100%). Two of these studies reported fair AUC[51,350] (75.2 and 79.8). One very low quality paper[54] (n=69) also reported a fair AUC of 74. One very low quality paper[109] (n=32) using a lower threshold (less than 26%) reported higher sensitivity (100%) and similar specificity (80%).

%HRC

Very low quality evidence based on raw data scores in two cohort studies[51,350] (n=157) using a more than 6% threshold showed reasonably high and variable sensitivity (point estimates of 82% and 92% with a range from 62-100%) and reasonably high and variable specificity (point estimates of 75% and 95% with a range of 51-99%). These studies also reported excellent AUC (93.7 and 92.9). One very low quality paper[54] (n=69) also reported a fair AUC of 72. One very low quality paper[109] (n=32) using a higher threshold (more than 10%) reported lower sensitivity (43%) and similar specificity (80%).

TSAT

Very low quality evidence from a diagnostic meta-analysis of six studies[51,93,109,110,332,350] (n=357) using a less than 20% threshold showed variable and mediocre sensitivity 61% (34-84%) and mediocre specificity 78% (63-91%). AUC from three of the six studies[51,332,350] (n=257) and one additional very low quality study[54] (n=69) not included in the meta-analysis ranged from very poor/equal to chance to good (40-90).

SF

Very low quality evidence from a diagnostic meta-analysis of six studies[51,93,109,110,332,350] (n=357) using a less than 100 micrograms/litre threshold showed low senility 39% (20-60%) and reasonably high specificity 81% (65-92%). AUC from two of the six studies[332,350] (n=225) and one additional very low quality study[54] (n=69) not included in the meta-analysis ranged from very poor/equal to chance to poor (38-69).

TSAT/SF combinations

Very low quality evidence from one study[63] (n=100) investigating the use of TSAT and SF alone or in combination (and/or) showed very low sensitivity 27% and high specificity 92%. Moderate quality evidence from a second paper[332] (n=100) investigating TSAT and SF in combination showed similarly low sensitivity 33% and high specificity 98%.

sTfR

Very low quality evidence from one cohort study[12] (n=17) showed reasonably high but highly variable sensitivity 82% (47-100) and specificity 78% (40-97). Very low quality evidence from two other studies[51,350] reported fair to excellent AUC (78.3 and 98.9).

Economic

An original cost–utility analysis that compared different test and treat strategies for treating iron deficiency in patients with anaemia due to CKD undergoing haemodialysis in hospital found that

- %HRC more than 6% was dominant (less costly and more effective) compared with all of the following strategies
  a. TSAT less than 20%
  b. SF less than 100 micrograms/litre
  c. SF less than 200 micrograms/litre
  d. CHr less than 29 pg
  e. TSAT less than 20% and/or SF less than 100 micrograms/litre
  f. TSAT less than 20% and SF less than 100 micrograms/litre.

This analysis was assessed as directly applicable with minor limitations.

An original cost–utility analysis that compared different test and treat strategies for treating iron deficiency in patients with anaemia due to CKD **not** undergoing haemodialysis found that

- %HRC more than 6% was cost effective compared to the following
  a. SF less than 100 micrograms/litre
  b. CHr less than 29 pg
  c. TSAT less than 20% and SF less than 100 micrograms/litre (ICER: £16,900 per QALY gained compared to c).
- %HRC more than 6% was dominant (less costly and more effective) compared to all of the following strategies
  d. TSAT less than 20
  e. SF less than 200 micrograms/litre
  f. TSAT less than 20% and/or SF less than 100 micrograms/litre

This analysis was assessed as directly applicable with minor limitations.

4.3.5 Recommendations and link to evidence

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	**Clinical effectiveness of diagnostic tests** For the clinical effectiveness review the important outcomes were related to erythropoietic response – ESA use to maintain target Hb and number of patients responding to iron therapy. Health-related quality of life was also an important outcome. No evidence was found in relation to Hb or quality of life patient-related outcomes. **Diagnostic accuracy** The GDG agreed that the critical outcome for diagnostic test accuracy was sensitivity of the index test relative to a reference standard of erythropoietic response as defined by study (which is assumed to give the 'true' diagnosis). Specificity was also agreed to be important to determine diagnostic test accuracy. Poor sensitivity may result in people with iron-deficiency anaemia being undiagnosed and therefore untreated.
Trade-off between clinical benefits and harms	The clinical evidence indicated that the use of %HRC using a >6% threshold showed reasonably high, although variable sensitivities and specificities. (Point estimates for sensitivity were 82% and 92% with a range from 62-100%; point estimates for specificity were 75% and 95% with a range of 51-99%). These studies also reported excellent AUC (93.7 and 92.9). However, the GDG noted that currently these tests are not as widely available as TSAT or SF. %HRC is available in 20% of hospitals.

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	The GDG agreed to recommend %HRC as they felt that the benefits of promoting this test, in spite of its limited availability, far outweighed any concerns. TSAT and SF were acknowledged to be the most commonly used tests. The clinical evidence from a diagnostic meta-analysis of six studies using a <20% threshold showed variable and mediocre sensitivity 61% (34-84%) and mediocre specificity 78% (63-91%) with the use of TSAT. Similarly for SF, evidence from a diagnostic meta-analysis of six studies using a <100 micrograms/litre threshold showed low sensitivity 39% (20-60%) and reasonably high specificity 81% (65-92%). Studies investigating the use of TSAT and SF alone or in combination with one another showed very low sensitivity (27%) and high specificity (92%)at the thresholds agreed by the GDG. The GDG discussed the implication of having false positives and false negatives in diagnostic tests. Poor sensitivity in a diagnostic test will result in more false negatives, which in turn will lead to people with iron-deficiency anaemia being undiagnosed and, therefore, untreated. In contrast, low specificity, leading to incorrect positive diagnoses (more false positives), will lead to unnecessary treatment, carrying a risk of unnecessary adverse events and higher costs. The GDG noted that as these tests are conducted quite frequently and regularly, it meant that neither false negatives nor false positives would continue to remain unchecked for long periods of time.
Economic considerations	The **cost of the different tests** varies between laboratories. However, it is likely that laboratory costs will be minimised by using %HRC, since it can be calculated from a FBC (using suitable analysers), which will already be routinely ordered for patients with CKD and anaemia. Even allowing for a SF test every 3 months for detecting iron overload this is still a low-cost test strategy. The **health economic model** compared various diagnostic methods, used to run a 'test and treat' regime. It did not specifically compare oral versus intravenous iron. The base case assumptions were 'conservative' (that is, if anything they were biased against the more sensitive test strategies, by overestimating the costs and the side effects of iron therapy). This included the following: • The underlying incidence of iron deficiency was assumed to be 10% per month, with sensitivity analyses using 0% and 20%, for both the non-haemodialysis patients and haemodialysis patient groups (the lower the incidence the more sustained are the benefits of iron therapy). • A treatment related SAE rate of 16% per patient for intravenous iron with all such SAEs requiring a day case or inpatient admission • Oral iron was considered for use in 25% of non-haemodialysis patients (50% in a sensitivity analysis), with a treatment-related SAE rate of 12% for oral iron • We assumed that 50% of non-haemodialysis patients receiving intravenous iron would receive low-dose high-frequency (that is, doses of <500 mg iron given over a number of visits) even though this is more costly than high-dose low-frequency. • We used the highest treatment discontinuation rate from the review[209] and assumed that everyone discontinuing treatment would remain iron deficient until the next routine test. List prices were used for intravenous iron (whereas we know it is often discounted). **Most cost-effective strategies** Two diagnostic **test strategies** used red cell markers of iron deficiency, and five strategies used serum markers of iron deficiency, singly or in combination. The

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	GDG looked to find tests performing reasonably well across both patient groups (haemodialysis; non-haemodialysis). Using different strategies for the two different populations is possible, but more complex for healthcare staff to operate. The QALY gain seen, even with the best strategy, was modest. **Three strategies performed relatively better** in the health economic analysis for both non-haemodialysis and haemodialysis patients: the two red cell markers and the combination of 'TSAT <20% and SF <100 micrograms/litre'. **%HRC > 6%** was both highly sensitive and specific. CHr < 29pg had lower sensitivity but good specificity; the combination had lower sensitivity but very high specificity. In the base case analysis, the two alternative strategies had similar costs to the optimal strategy (%HRC), but a minor reduction in mean QALYs. The strategies were ranked 1-3 in the base case analysis for both sub-populations and one of them was ranked first in every sensitivity analysis. **Practical issues with %HRC** %HRC>6% was both sensitive and specific, based on the Tessitore 2001[350] paper. The GDG noted that this study (the larger of the two) processed the FBC specimens within three hours, avoiding artefactual red cell swelling which can give a false positive result. The GDG noted that, to maintain the specificity of the test, FBC specimens should be processed quickly (within 6 hours). There were concerns that satellite dialysis units might transfer FBC specimens to a laboratory on a next day basis, particularly for patients dialysing during an evening or 'twilight' shift. If analysing the test within 6 hours is not possible, then CHr becomes the more appropriate test. The majority of UK laboratories are capable of providing one of the red cell or reticulocyte tests. Alternative strategies, when %HRC was not available, included CHr <29 pg (or equivalent, for example, RetHe) and the combination of 'TSAT <20% and SF <100 micrograms/litre'. The GDG felt that Renal and Haematology departments should collaborate over future plans for development of red cell analysers, bearing the above issues in mind. They also noted that it would be important that laboratories collaborate with manufacturers of the analysers and the appropriate quality assurance scheme organisations such as UK NEQAS (United Kingdom National External Quality Assessment Service) to provide users with both internal and external quality assured results for the red cell and reticulocyte analytes. **Least cost-effective strategies** Four strategies performed poorly in the health economic analysis: SF alone (at cut-offs of 100 or 200 micrograms/litre), TSAT alone, and the strategy of using either low ferritin or low TSAT as an indicator for intravenous iron therapy. Two test strategies with low specificity (SF <200 micrograms/litre; 'TSAT <20 and/or SF <100 micrograms/litre'), utilised more iron with minimal gain in mean QALYs (due to futile treatment, and adverse effects). Two strategies with lower sensitivities (SF <100 micrograms/litre alone; TSAT <20% alone), used less iron, but with poorer mean QALYs (due to false negative tests and the effect of untreated patients). The GDG noted that clinicians may not, to date, have fully realised the implications of using ferritin when, depending on the cut-off used, it is a low sensitivity or low specificity indicator of iron deficiency in CKD. There are similar considerations for the use of TSAT alone as a marker of iron deficiency. The GDG noted the failure as a testing strategy of ferritin alone (at either cut-off value) or TSAT alone, hence the 'do not use' recommendation. This will be a significant change in UK practice, which the GDG strongly felt should be implemented due to the evidence discussed above.

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	Consideration of uncertainty Some of the parameters in the analysis were uncertain and therefore, sensitivity analysis was conducted. Only in the following quite extreme circumstances was %HRC no longer cost-effective for non-haemodialysis patients: • When we assumed 1.4% of SAEs were fatal (based on EMA report[102]) and no survival benefit from achieving target Hb, then, the quality of life benefits from iron were outweighed by the risks (for both haemodialysis and non-haemodialysis patients). We think this unlikely, since there is no evidence that iron therapy reduces survival in CKD patients and by following the MHRA recommendations[221], the risks will be minimal. In this context, the GDG noted the crucial importance of minimising the risks of intravenous iron. This was felt to further emphasise the need to follow the MHRA recommendations in their entirety. In the model, we have costed intravenous iron therapy in a hospital context with 30 minutes post-infusion observation time to allow compliance with the MHRA guidance. • When we used the cost of a day case from the NHS reference costs for each iron therapy visit for non-haemodialysis patients. Then the costs of iron therapy (specifically low-dose high-frequency) were too high for iron therapy to be cost-effective. However, iron therapy is often delivered as a less costly outpatient visit rather than a day-case. • When we use the accuracy data from Bovy 2007[51] instead of the data from Tessitore 2001[350] for %HRC>6% (for both the haemodialysis and non-haemodialysis subgroups). However, the Tessitore study was a larger study with 125 patients. Tessitore reported that %HRC was analysed within 3 hours of collection of blood sample. Bovy 2007 included only 32 patients and the time between blood sample collection and testing was not reported. Hence, data from the Tessitore 2001 study was agreed to be more reliable (see note above about 'practical issues' for use of %HRC). In all other sensitivity analyses, %HRC <6% was the most cost-effective strategy. Furthermore, as noted above, we have been, if anything, biased against more sensitive test strategies by potentially over-estimating the cost and side effects of iron. Had we been less conservative, then %HRC would have appeared even more cost-effective compared with the combined strategy of 'TSAT <20% and SF <100 microgram/litre'. Therefore, we conclude that where %HRC is available and can be processed quickly this is the optimal test. However, given the practical issues we have noted above, we recommend the following tests where %HRC is not possible: CHr (or equivalent) <29 pg, or the test combination of 'TSAT <20% and SF <100 micrograms/litre'.
Quality of evidence	Evidence of the clinical effectiveness of tests based on ESA use ranges from moderate to low quality. This is based on the industry funding provided for both the studies and uncertainty around the effect of one of the two studies resulting in downgrading due to imprecision. There was sufficient data to do a diagnostic meta-analysis on two of the available tests, TSAT and SF. The evidence for both these tests was graded as very low quality. This was due to serious limitations in research design relating to selection bias, serious inconsistency and serious imprecision around the pooled sensitivity and specificity summary point. For each of the remaining tests, there were less than five studies reporting information for each so it was not possible to conduct meta-analyses. The evidence for the remaining tests ranged from low to very low quality. This was

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	again predominantly due to issues of patient selection, and serious or very serious imprecision around the individual point estimates for each test per study. Evidence relating to CHr and %HRC from one study which reported on higher thresholds was also further downgraded for indirectness. Only two studies were identified which provided information on test combinations. Both of these looked at TSAT and SF, but one used both and another used an and/or protocol. The evidence ranged from moderate to very low quality due mostly to imprecision. The recommendation for the test intervals (once every 3 months) was based on the consensus expert opinion of the GDG.
Other considerations	The GDG wished to understand which test or combination of tests was most accurate at predicting response to iron therapy. However, it was also acknowledged that evaluating response to iron therapy is not independent of first assessment of iron status and the same tests need to be viewed in a continuum throughout diagnosis, monitoring and maintenance. It was noted that the person may not necessarily enter the pathway at the point of an initial diagnosis of iron deficiency. Indeed, many patients in the studies included in this review had received iron therapy previously and were receiving maintenance therapy; therefore the distinction of patients into diagnostic and maintenance was arbitrary and the tests were applicable at all stages. As a result, the recommendations emerging from this evidence review impact upon and, in part, replace the recommendations made previously in CG39 which relate to maintenance and monitoring of iron status in patients who were receiving ESA therapy (see table in Appendix R for recommendations from previous versions of the guideline that have been deleted or amended with the reasons for the changes). The GDG noted that the laboratory tests reported reference range is for normal, non-CKD patients. While our population was restricted to CKD patients, the tests work the same way in the wider non-CKD population. SF levels can be raised in chronic inflammation, whereas the reticulocyte markers are not affected by inflammatory states. Haemodialysis patients tend to have a chronic inflammatory response which artefactually raises SF levels. In haemodialysis patients, however, regardless of whether a SF threshold of 100 or 200 is used, it is still likely that iron therapy will be given. The GDG noted that patients with CKD 1 and 2 may not have chronic inflammation, and so will not be that different from populations with other diseases that may be testing for anaemia. However, in the general population, these tests are done purely to diagnose iron deficiency, whereas in people with CKD, the GDG noted that the tests are used more to guide management of treatment. Therefore, pure diagnostic accuracy research would be helpful in general, but for a specific CKD population knowing the clinical effectiveness of the diagnostic tests would be more beneficial. Reflecting the population of the evidence we found, the GDG noted that most new studies are undertaken in haemodialysis patients. The GDG noted that the laboratory tests that are available fall into two broad categories: those that represent the storage and movement of iron within the body, such as SF and TSAT, respectively, and those tests that represent the end result of iron usage within the bone marrow, for example, mean corpuscular Hb, %HRC and CHr. The important aspect to realise is that even when there are apparently normal 'stores' this does not mean that it is available to developing red blood cells. Dealing with each in turn below, the GDG noted the following: **%HRC** use is becoming more widely available with approximately 20% of laboratories in the UK currently able to perform this test. However, it needs to be analysed within 6 hours of the sample being taken, because swelling of the red

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	cells can occur after 24 hours leading to erroneous results. This is of particular concern if the test sample is being transferred, for example in satellite units and when the test is performed during the 'twilight' shift. The GDG also noted that testing of %HRC will give erroneous results in people with thalassaemia or thalassaemia trait and recommended alternative tests in this group. This is because irrespective of having iron deficiency, %HRC is increased in this population thalassaemia or trait is characterized by small red blood cells with low haem content. So testing for %HRC will over-diagnose iron deficiency. **CHr/Ret-He** is currently available with the GDG estimating that over 50% of UK labs would have access to one of these analytes. It has not, however, featured strongly in any existing guidelines so there has been no strong clinical imperative to use it to date. CHr also needs to be done in a timely manner as RNA in the reticulocyte starts to degrade in vitro, and some of the reticulocytes may no longer be counted as such over time. This is an important consideration for satellite units and tests performed during the 'twilight' shift. Next day testing is acceptable, but because transport delays are less of an issue for CHr compared with %HRC. As with %HRC, CHr/Ret-He are also not indicated in patients with thalassaemia or thalassaemia trait as Ret-He and CHr are lowered by the presence of thalassaemia trait, and indeed Thalassaemia intermedia and major (which has its iron overload problems).[55] **TSAT** is a cheap and readily available test. TSAT measures storage and transport, but not the potential utilisation of what is stored. Based on limited sensitivity and specificity observed from the diagnostic meta-analysis, the GDG recommended against the use of TSAT in isolation for the diagnosis of iron deficiency. **SF)** is a cheap and readily available test. SF is currently used for diagnosis of iron deficiency and iron overload. The GDG were concerned about the widespread use of SF alone for diagnosis of iron deficiency given that it demonstrated very low sensitivity (39%, pooled meta-analysis data). The GDG agreed that, while it was still useful to test for iron overload (when SF levels are greater than 800 micrograms/litre), SF was not very useful to test for iron deficiency and recommended against its use. The GDG recommended its use for diagnosis of iron deficiency only in combination with TSAT and when other sensitive tests (%HRC, CHr) were not available. **sTfR** There is extremely limited and low quality evidence for this test. It is the GDG's understanding that it is not widely used, is not readily available and is expensive so was therefore not included in the economic model. There was very little evidence identified on combinations of tests. Two studies looked at different combinations of TSAT and SF, showing very low sensitivity and high specificity. In a particular sub-group of patients (those with high ferritin, for example, >200 [GDG consensus]), the GDG recognised that the use of TSAT and SF together is current practice in some units in the UK. The GDG perception is that if TSAT <20-30% [GDG consensus about current practice] then clinicians would give iron therapy. The combination of TSAT and SF was recommended for diagnosis of iron deficiency only if other more sensitive tests were not available. There was no evidence for diagnostic testing of iron deficiency in children. **Summary:** Based on the evidence (ranging from low to very low quality) which showed that %HRC had high sensitivity and specificity, followed by CHr, and the results of the health economic model, the GDG recommended %HRC (>6%) as the first-line test to diagnose iron deficiency followed by CHr or equivalent test (<29 pg). TSAT (<20%) and SF (<100 micrograms/litre)in combination were only recommended for

Recommendations	1. The current recommendations can be found at www.nice.org.uk/guidance/ng203
	the diagnosis of iron deficiency when any of the other tests were not available; the GDG agreed that as the sensitivity for each test was very low, neither TSAT nor SF could be used for diagnosis of iron deficiency and recommended against their use in isolation. However, it was acknowledged that SF still has a place in the diagnosis of iron overload (SF >800 micrograms/litre) and should be used (link to CG114 recs and algorithm). **Withdrawn recommendations** The following four recommendations from the 2006 guideline were withdrawn as part of the 2015 update, since the GDG wished to de-prioritise the use of serum ferritin in favour of tests that more accurately predict response to iron therapy. 1. In non-dialysis patients with anaemia of CKD in whom there is evidence of absolute or functional iron deficiency, this should be corrected before deciding whether ESA therapy is necessary. 2. Serum ferritin levels may be used to assess iron deficiency in people with CKD. Because serum ferritin is an acute-phase reactant and frequently raised in CKD, the diagnostic cut-off value should be interpreted differently to non-CKD patients. 3. Iron-deficiency anaemia should be : • diagnosed in people with stage 5 CKD with a ferritin level of less than 100 micrograms/litre • considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 micrograms/litre. 4. In people with CKD who have serum ferritin levels greater than 100 micrograms/litre, functional iron deficiency (and hence, those patients who are most likely to benefit from intravenous iron therapy) should be defined by: • percentage of hypochromic red cells greater than 6%, where the test is available or • transferrin saturation less than 20%, when the measurement of the percentage of hypochromic red cells is unavailable. [2006]

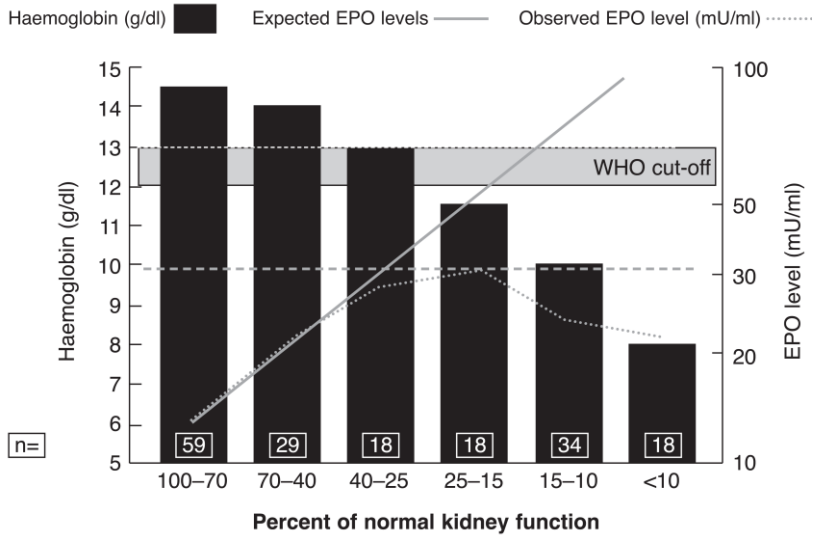
4.4 Measurement of erythropoietin [2006]

4.4.1 Clinical introduction

Although anaemia in CKD may develop in response to a wide variety of causes, erythropoeitin (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 6).

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[25]. 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% at an estimated GFR of 60 ml/min per 1.73 m2, to 9 and 33% 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[100]. In a study of 5,380 participants from the Kidney Early Evaluation

Figure 6: Evolution of anaemia in CKD (Reproduced with kind permission of Dr Anatole Besarab).



EPO = erythropoietin; WHO = World Health Organization.

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[353].

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%[352].

In patients with less advanced CKD there may be some uncertainty about 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 EPO levels may be beneficial and the evidence review in this section seeks to address this.

4.4.2 Methodological introduction

One cohort study[292], six cross-sectional studies[14,50,97,104,233,352] and two longitudinal studies, prospective[59] and retrospective[76], which examined the association between serum erythropoeitin with Hb levels or renal function, were identified in a literature search.

Notable aspects of the evidence base were:

- 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[76], selected people with Type 1 diabetes with diabetic nephropathy in the absence of advanced renal failure[50], people with Type 1 and 2 diabetes[352].
- Other causes of anaemia were explicitly ruled out in some studies[50,59,76,104,292].
- Where reported, anaemia was defined as <13 g/l for men and <11.5 g/l for women[76], Hb ≤11.5 g/dl for women and 12.0 g/dl for men[50], Hb <11 g/dl[104], Hb <12 g/dl for women and Hb <13 g/dl for men[352].

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

In people with Type 2 diabetes without nephropathy (n=62) a significant negative correlation between serum EPO and Hb levels was found (r2=0.612, p=0.01)[76]. (Level 3)

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[50]. (Level 3)

A cross-sectional study conducted in people with diabetes[352] 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/1.73m2 or >90 ml/min/1.73m2. (Level 3)

In a subgroup of iron replete diabetic patients (transferrin saturation level >16%), from the above study[352], serum EPO levels did not change significantly with Hb level as shown below.

Table 43: Characteristics in anaemia and raised or normal serum EPO (Level 3)

	No anaemia, n=554	Anaemia + normal EPO, n=131	Anaemia raised EPO, n=37
Erythropoietin (IU/l)	15 ± 8	16 ± 7	74 ± 112*#
Haemoglobin (g/dl)	14.1 ± 1.1	11.6 ± 1.0*	11.0 ± 1.1*#
GFR (ml/min/1.73m2)	79 ± 26	57 ± 28*	66 ± 28*#
TSAT <16%	15%	31%*	73%*#
* Vs no anaemia p<0.05.			
# Vs anaemia with normal levels of EPO.			

Children with chronic renal failure

No significant correlation was found between serum EPO and Hb/Hct levels in three studies conducted in children with chronic renal failure (n=7[14]; n=10[97]; n=37[59]). (Level 3)

Likewise, no significant correlation was found between serum EPO levels and renal function assessed by means of eGFR (n=37)[59] or serum creatinine (SCr) (n=30)[233] in children with chronic renal failure. (Level 3)

The results of a study which investigated Hb and serum EPO levels in children with chronic renal failure and healthy children are shown in Table 44.

Table 44: Hb and serum EPO in children (Level 3)

	N	Hb (g/dl)	Mean serum EPO (U/l)
Predialysis	30	10.7 ± 2.5	36.2 (range 7 to 235)
Post-transplant	15	11.6 ± 2.6	39.5 (range 10 to 125)
Healthy children	20	13.2 ± 0.8	35.2 (range 18 to 64)

Adults with chronic renal failure on conservative therapy

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 with healthy controls (n=59) ($p<0.01$). In a subgroup analysis of patients with CCr 2–40 ml/min/1.73m2 (n=88), CCr and serum EPO showed a positive correlation ($r=0.27$, $p<0.015$)[292]. (Level 2+)

Unselected population of adults

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[104]. (Level 3)

4.4.4 From evidence to recommendations

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.

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 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5 Management of anaemia

5.1 Initiation of ESA therapy in iron-deficient patients [2006]

5.1.1 Clinical introduction

Iron management forms an essential part of the treatment of anaemia associated with CKD and availability of iron is of key importance for iron 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 1,500 to 5,000 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.

In health, iron is almost completely recycled and losses are of the order of 1 mg/day, requiring minimal replacement. Iron deficiency is the most common cause of anaemia worldwide. 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 3,000 mg iron per year. In the first 3 months of ESA therapy it is estimated that a haemodialysis patient needs an extra 1,000 mg of supplemental iron, underlining the importance of adequate availability of iron for optimal erythropoiesis[40].

5.1.2 Clinical methodological introduction

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

One study met methodological criteria[313]. 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 less than 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[313].

5.1.4 Health economic evidence statements

The study found that intravenous iron dextran saved approximately Canadian $63 per patient ($3,016 total) from EPO savings and oral iron savings in 50 patients. However, the initial cost of i.v. iron dextran loading was $3,426 in the first year. Therefore, the loading dose of i.v. iron dextran offset 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 (Canadian $, 1996) per year in the 50 patients in the study with $30,120 of EPO savings per year and $2,738 from oral iron savings per year[313].

5.1.5 From evidence to recommendations

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 GFR 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

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.2 Maximum iron levels in patients with anaemia of CKD [2006]

5.2.1 Clinical introduction

Iron is crucial for survival and is necessary for erythropoiesis and the production of usable energy through oxidative phosphorylation. However, iron-overload states are harmful and the potent oxidising ability of non-transferrin bound iron makes it potentially toxic. 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. 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 about 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 antioxidants 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

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

Because of the lack of evidence, it was agreed that an upper limit of 800 µg/l of ferritin should be used in line with the current European Best Practice Guidelines[b]. This level is drawn from data on iron toxicity studies performed in the pre-ESA era that demonstrated that high ferritin levels >1,000 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 are any long-term consequences related to the administration of intravenous iron as this route bypassed normal absorption routes and homeostatic mechanisms.

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.

b At the time of writing the current European guidelines were: European best practice guidelines for the management of anemia in patients with chronic renal failure. *Nephrology Dialysis Transplantation* 1999;14(Suppl 5):1-50.

5.2.4 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.3 Clinical utility of ESA therapy in iron-replete patients [2006]

5.3.1 Clinical introduction

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 the potential number requiring anaemia management is 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.

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 and 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

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

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 subgroups of patients in whom the administration of ESAs may be of little clinical benefit.

The GDG discussed whether they considered there were any patient subgroups with a Hb level below 11 g/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 (eg presence of comorbidities), as to whether a patient would benefit from the administration of ESAs.

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.

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 a patient may gain from ESA therapy, a trial of ESA therapy and assessment of response may be indicated prior to

continuing long-term treatment. The GDG felt that the patient was a good judge of whether the treatment had any noticeable improvement on their quality of life 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

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.4 Nutritional supplements [2006]

5.4.1 Clinical introduction

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 functions of many vitamins.

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 about 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-dependent population, excluding predialysis patients.

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.

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 practice supplementation with fat soluble vitamins is not recommended.

Data remain incomplete on individual requirements of vitamins, the handling of vitamins in uraemia, the vitamin status of uraemic patients and the effect of vitamin administration.

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 practice, this is not done routinely.

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

A comprehensive literature search identified eight studies. Of these, two studies addressed vitamin C: a cross-over RCT[134] and a non-randomised controlled trial[343]. One RCT addressed folic acid[261]. Five studies addressed carnitine supplementation, which consisted of three RCTs,[56,174,180] a cross-over RCT[311] and a before and after study[198].

Eleven studies had methodological limitations and were thus excluded from the evidence statements. These include four which addressed vitamin C,[171,315,344,346] one which addressed vitamin E[251], one which addressed folate[173], and five which addressed carnitine supplementation[148,214,305,328,361].

Notable aspects of the evidence base were:

- No studies addressing vitamin E or glutathione were found.
- The meta-analysis investigating carnitine supplementation[148] did not meet quality criteria, hence the studies within it[56,174,180] were individually appraised.
- One study was conducted in children[198].
- One study[134] was conducted in a pre-selected patient population.

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

A non-randomised trial (n=52)[343] 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 eight domains of quality of life assessed using the Short-Form 36 (SF 36) scale. (Level 2+)

In a randomised controlled trial (RCT) of cross-over design (n=27)[134], where ascorbic acid 1,500 mg/week was administered i.v. for 3 months, Hb increased ($p<0.01$ in group I and $p<0.005$ in group II) and TSAT increased (both group I and group II $p<0.001$), whereas ferritin decreased ($p<0.004$ in group I and $p<0.001$ in group II) when compared with baseline levels. Epoetin doses, however, remained unchanged in both groups. (Level 1+)

Folic acid

Haemodialysis patients

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 increased further (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[261]. (Level 1+)

Carnitine

Haemodialysis patients

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 period. Similarly, no differences were observed in epoetin dose or Hb levels[311]. (Level 1+)

No differences were observed in epoetin dose requirement or Hct and reticulocyte counts in a 6-month 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[56]. (Level 1+)

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[180]. (Level 1+)

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[174]. (Level 1+)

Paediatric haemodialysis and peritoneal dialysis patients

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), with a mean age of 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[198]. (Level 3)

5.4.4 From evidence to recommendations

It was concluded that there was no evidence to support the adjunctive 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 predialysis population. It was considered acceptable to extrapolate the conclusions to the predialysis population.

With regard to vitamin C, the appraised studies administered very high doses (1,500 mg/wk, 1,000 mg/wk and 100 mg/wk). A dose of 50 mg/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 of iron and promoting effective erythropoiesis. The evidence base was small.

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

5.4.5 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.5 Androgens [2006]

5.5.1 Clinical introduction

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[58,89,123,144,377] 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[234]. However, their regular use was abandoned because of 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.

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

5.5.2 Methodological introduction

A literature search identified eight studies, including two RCTs[132,248], three cohort studies[32,348,349] and one before and after study[185].

Two studies[39,131] had methodological limitations and were therefore excluded from the evidence statements.

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.

Notable aspects of the evidence base were:

- The studies were investigating:
  - epoetin vs nandrolone[248,349]
  - epoetin vs epoetin and nandrolone[32,132]
  - epoetin and nandrolone (no control group)[185]
  - Nandrolone alone (no control group)[348].
- Although side effects were noted in some studies[132,185,348], the authors did not attempt to quantify all of these.
- The studies were conducted in both male and female patients except for two studies[32,248], which were conducted solely in male patients.

5.5.3 Evidence statements

Hb/Hct levels

Haemodialysis patients

In a before and after study conducted in male (n=9) and female (n=8) patients[185], 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)

In a cohort study conducted in male (n=67) and female (n=17) patients[348], Hb and Hct levels rose (both p<0.01) following 6 months' therapy with nandrolone decanoate 200 mg i.m. weekly. 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 the following:

- 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)
- 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 less than 46 years (n=29), 46–55 years (n=28) and more than 55 years (n=27), only the latter two groups showed improvement in Hb levels (both p<0.01) following androgen therapy. (Level 2+)

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)[349]. (Level 2+)

In a cohort study[32] 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+)

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 men and 6 women) and nandrolone 100 mg i.m. once a week (n=9; 7 men and 2 women) over 26 weeks found a significant increase in Hct in both treatment groups when compared with 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 with epoetin alone[132]. (Level 1+)

CAPD patients

Hb and Hct levels increased in both treatment groups in a RCT[248] 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 with baseline values. However, these increases in Hb and Hct levels were not significantly different when the treatment groups were compared with each other. (Level 1+)

Epoetin dose

Haemodialysis patients

In a before and after study conducted in male (n=9) and female (n=8) patients[185], weekly epoetin doses following adjuvant therapy with nandrolone decanoate (100 mg i.m. weekly for 6 months) did

not change significantly, either in the overall cohort or when stratified into male and female patients. (Level 3)

In a cohort study conducted over 12 weeks in male patients treated with epoetin (6,000 U i.v. three times a week) (n=7) vs epoetin (6,000 U i.v. three times a week) and nandrolone decanoate 100 mg i.m. once a week (n=8), no difference was observed in epoetin dose between the two treatment groups[32]. (Level 2+)

Adverse events—serum triglycerides

Haemodialysis patients

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[348]. (Level 2+)

A 6-month cohort study conducted to compare the effect of nandrolone decanoate (200 mg 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 ($p<0.001$)[349]. (Level 2+)

5.5.4 From evidence to recommendations

The rationale for the administration of androgens to patients with anaemia of CKD was historical in that androgens were administered in the pre-ESA 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 in that the administration of androgens could reduce the dose of ESA required but were concerned about the potential side effects and considered this an outdated approach to anaemia management.

5.5.5 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.6 Hyperparathyroidism [2006]

5.6.1 Clinical introduction

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)[295,330,362]. Elevation of PTH in the stage 3 and 4 CKD populations predicts the development of more severe hyperparathyroidism, which in turn is clearly associated with increased skeletal and cardiovascular morbidity and mortality[83]. 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 erythropoietin 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

A literature search identified seven studies. These consisted of a cohort study[83], a two-part study comprising a cohort study and prospective before and after study[199], a two-part study comprising a prospective longitudinal study and cohort study[137], a prospective before and after study and cohort study[386], a prospective longitudinal study[18], and two retrospective before and after studies[68,294].

Six studies[35,126,250,286,364,388] had methodological limitations and were therefore excluded from the evidence statements.

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.

Notable aspects of the evidence base were:

- Treatment for parathyroidism was stratified into drug-based with calcitriol[137,199], alfacalcidol[18], or surgery[68,83,184,294].

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 45: Summary of evidence for appraised studies

Reference	Drug-based therapy	Sample size	Baseline iPTH levels (pg/ml)	Treatment duration	Outcome	Effect	Level of evidence
[199]	Calcitriol 2 µg	n=16	778 ± 172.7	6 months	n=7 responders		Level 2+
					iPTH	↓	
					Hct	↑	
					Epoetin dose	↓	
[18]	Alfacalcidol 6 mg	n=12	~475	18 months	iPTH	↓	Level 3
					Hb	↑	
[137]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Hb/Hct	↑	Level 3
					IPTH	↓	
[137]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Epoetin use (n=21) vs No Epoetin	No change	Level 2+

Reference	Drug-based therapy	Sample size	Baseline iPTH levels (pg/ml)	Treatment duration	Outcome	Effect	Level of evidence
					(n=7) Epoetin dose		
[137]	Calcitriol i.v. 2 µg	n=28	811.6 ± 327	12 months	Responders (n=19) vs non-responders (n=9)		Level 2+
					Hct	↑	
					Epoetin dose	No change	
Author/Study ID	**Surgical procedure**	**Sample size**	**Basal iPTH levels (pg/ml)**	**Length of follow-up after surgery**	**Outcome**	**Effect**	**Level of evidence**
[294]	Subtotal parathyroidectomy (n=9) and total parathyroidectomy with forearm autotransplantation (n=1)	n=10	Not reported	6 months	iPTH	↓	Level 3
					Hct	↑	
					Epoetin dose	↓	
[199]	Total parathyroidectomy with forearm autotransplantation	n=3	976 ± 436.1	6 months	iPTH	↓	Level 3+
					Hct	↑	
					Epoetin dose	↓	
[68]	Subtotal parathyroidectomy	n=19	1,726 ± 1,347	1–2 years (n=44)	Hb	No change	Level 3
	Total parathyroidectomy and autotransplantation	n=10	913 ± 380	3–5 years (n=24)	Hb	↑	
	Total parathyroidectomy	n=10	1,006 ± 668				
	Partial parathyroidectomy (removal of 2–3 parathyroid	n=6	1,176 ± 3346				

Reference	Drug-based therapy	Sample size	Baseline iPTH levels (pg/ml)	Treatment duration	Outcome	Effect	Level of evidence
	glands)						
[386]	Total parathyroidectomy and forearm autotransplantation	n=29 Note n=7 underwent reoperation for recurrences in neck and forearm	873 ± 710.8	12 months	iPTH	↓	Level 3
					Hb	↑	
					Plasma erythropoietin	↑	
				12 months	Epoetin use (n=23) vs No Epoetin (n=6) Epoetin dose	No change	Level 2+
[184]	Total parathyroidectomy and forearm autotransplantation	n=32 1,338 ± 350.6	Responders Non-responders 1,228 ± 290.8	3 months	n=17 responders (≥10% Hb increase post-PTX) vs n=15 non-responder	No change No change No difference	Level 2+
					Hb Serum erythropoietin	↓ but no difference between the 2 groups	
					iPTH		
↑ = significant increase;							
↓ = significant decrease;							
PTX = parathyroidectomy.							

5.6.4 From evidence to recommendations

Treatment of hyperparathyroidism secondary to CKD is part of good clinical practice as is routine monitoring of PTH levels in patients with CKD. Early control of hyperparathyroidism is crucial for preventing metabolic bone disease and treating hyperparathyroidism is beneficial to anaemia management. The strategies used do not differ in patients with CKD whether they are anaemic or not. On the evidence available, it was not felt to be appropriate to recommend specific interventions and the British[297], American[213] and European[3] treatment guidelines in the management of renal osteodystrophy which are aimed at attainment of target PTH, calcium and phosphate concentrations should be followed.

5.6.5 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.7 Patient-centred care: ESAs [2006]

5.7.1 Clinical introduction

The ESAs currently available in clinical practice differ in terms of frequency of administration and route of administration. The ESAs currently available in clinical practice may be administered either subcutaneously or intravenously. Darbepoetin is likely to require less frequent administration than the erythropoietins, while the erythropoietins are likely to require less frequent administration and a lower dose when administered subcutaneously vs 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.

Key considerations for patients with anaemia associated with kidney disease are that:

- ESAs are prescribed when clinically indicated.
- The ESA supply, route of supply and storage arrangements are clearly defined, secure and convenient.
- The administration and monitoring of anaemia treatment is as efficient, comfortable and least disruptive as possible.

5.7.2 Methodological introduction

Seven studies were identified, including two RCTs[139,232], one of which was of cross-over design[139], one retrospective longitudinal study[373], one retrospective case series[255], and three cross-sectional studies[24,210,247].

One study[31] had methodological limitations and was thus excluded from the evidence statements. The buffer used in the preparation in the cross-over study[139] is no longer used, and the paper was therefore not considered further.

Notable aspects of the evidence base were:

- The studies conducted using questionnaires were limited by the use of closed questions in their design[210,247,373], with the exception of one study[24], which reported the use of both closed and open questions.
- All the studies using questionnaires were cross-sectional, with the exception of one study[373], which was of longitudinal design.

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

In a 24-week cross-over study[232] where s.c. was compared with i.v. administration, quality of life assessed by means of the Kidney Disease Questionnaire (KDQ), which consists of five domains, found improvements from epoetin administration (both intravenous and subcutaneous) in the physical ($p<0.05$) and fatigue ($p<0.05$) domains, but no significant differences between the two modes of administration in any other domains[139]. (Level 1+)

Adherence and ESA administration

Peritoneal dialysis patients

In a retrospective longitudinal study[373], 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 commonly reported reason being forgetfulness. Missing dialysis exchanges, completion of secondary education and younger age were found to be independent predictors of non-adherence (r2=0.36). (Level 3)

In a retrospective study[255], 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 ESA on behalf of the patient was the only significant correlation with concordance (r=0.46, p=0.005). (Level 3)

Haemodialysis and continuous ambulatory and automated peritoneal dialysis patients

In a cross-sectional study[210], concordance ranged from 24–33%, with the over-60 age group least likely to miss an epoetin dose and reduced frequency of administration associated with less missed doses. The majority of patients were likely to self-administer. Fewer injections were preferred by 72.5%, with the under-60 age group preferring once-weekly because of convenience, pain on injection and epoetin storage. (Level 3)

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[24], 57 of 86 (66%) patients reported they never missed doses, while 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. (Level 3)

Communication and obtaining of ESA

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[24], 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 a community pharmacy (n=63). (Level 3)

Predialysis, dialysis and transplant patients

In a cross-sectional study[247], 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%). (Level 3)

EPO administration – effect on quality of life

Predialysis, dialysis and transplant patients

In a cross-sectional study[247], 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'. (Level 3)

5.7.4 From evidence to recommendations

The evidence from seven studies contained outcome data on quality of life, pain, concordance, obtaining ESAs and communication with patients.

The data supported the view that patient preferences and experiences should be taken into account, where possible, when decisions are reached about 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 (for example, 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[255,373]. 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[210]. 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 healthcare providers to ensure adequate drug supply and storage facilities for patients.

5.7.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.8 Patient education programmes [2006]

5.8.1 Clinical introduction

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.

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

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

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.

Patient education should meet the individual needs of each patient and five themes drawn from recent work in the area[303] were considered to be important:

- practical management of anaemia
- knowledge (about symptoms, iron and ESA management and 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 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6 Assessment and optimisation of erythropoiesis

6.1 Benefits of treatment with ESAs [2006]

6.1.1 Clinical introduction

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 and 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

Four studies were identified. A meta-analysis (epoetin vs placebo or no treatment)[67], two multisite RCTs (epoetin vs placebo)[1,256], one cohort study (epoetin vs no treatment)[66] and a retrospective longitudinal study[288]. Two studies[29,288] had methodological limitations and were therefore excluded.

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

Notable aspects of the evidence base:

- All studies except for two included in the meta-analysis[67] did not explicitly state if they used epoetin-alfa or epoetin-beta.
- The study durations ranged from 12 weeks to 3.5 years.
- Studies included in the meta-analysis[67] achieved a lower Hb level and excluded patients with significant comorbidities.
- In one study[256] red cell transfusions were given to placebo or treatment arms when required.

6.1.3 Clinical evidence statements

Quality of life

Predialysis patients

Of the studies in the meta-analysis[67], 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 increased energy (p=0.045). However, the number of domains assessed in this study was not provided by the authors. (Level 1+)

Haemodialysis patients

In one study[1] 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 did not change significantly. (Level 1+)

Mortality

There were insufficient mortality data available from the meta-analysis[67] and the RCT[256] to write evidence statements.

Hospitalisation

Study participants new haemodialysis patients

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[66]. (Level 2+)

6.1.4 Health economics methodological introduction

Three studies were identified[188,296,334]. One study[225] did not meet met quality criteria and therefore no evidence statements were made.

One study contained a cost-effectiveness analysis before and during epoetin therapy[334]. It was predominantly a cost-savings analysis with 1990 to 1991 UK£ and earlier costs. However, the 1990 to 1991 or earlier cost data meant that there was insufficient data from which to derive evidence statements for application to the current NHS context.

One study compared cost per QALY results in five European countries including the UK[188]. This study used QALYs as the effectiveness measure. Nevertheless, costs were derived from 1988 values, which indicates there are insufficient data from which to derive evidence statements for the current NHS context.

An additional study[296] evaluated the cost per QALY of epoetin using the same framework as the Leese study[188] (1988 values), but updated data with values from the year 2000 in the UK.

6.1.5 Health economics evidence statements

The cost per QALY of ESA therapy 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 occurred, the cost per QALY would increase to £74,876[296].

6.1.6 From evidence to recommendations

One study[67] 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 evidence was not sufficient to make a sound evidence statement.

The GDG concluded that the study of people receiving peritoneal dialysis[256] did not contribute meaningful data as the study duration was too short (12 weeks) to assess mortality.

Of the outcomes assessed, the GDG felt there was only good evidence supporting improvement in quality of life through ESA therapy. 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[67] achieved a low target haemoglobin and the patients that may have shown the greatest benefits were excluded from the studies.

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 patient populations observed in clinical practice.

The GDG concluded on the basis of qualitative data and clinical experience that ESAs are of value.

Health economic evidence 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[296]. 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 underestimated the benefit of the treatment (n=24)[188]
- were based on a study design that could introduce bias[225], or
- were based on historical cost data that no longer had relevance to the current NHS context[334].

6.1.7 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.2 Blood transfusions [2006]

6.2.1 Clinical introduction

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

Data concerning adverse transfusion events in the UK are 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 an increase in the number of adverse transfusion incidents reported with now over 2,000 recorded in the SHOT database (Table 46). 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 and G, human immunodeficiency virus (HIV), human t-lymphocytotrophic 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 46: Serious Hazards of Transfusion (SHOT) Report 2003

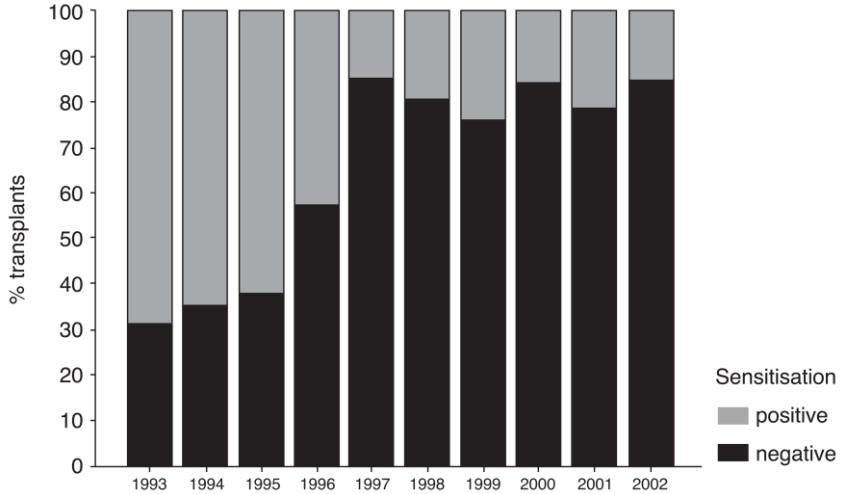
SHOT category	Reported cases 1996–2003, n (%)	Risk category	Estimated risk
Incorrect blood component transfused	1393 (66.7)	Risk of incorrect blood component transfused	1 in 16,500
Acute transfusion reaction	233 (11.2)	Risk of ABO incompatibility	1 in 102,200
Delayed transfusion reaction	213 (10.2)		
Transfusion-related acute lung injury	139 (6.7)	Risk of transfusion-related acute lung injury	1 in 165,000

SHOT category	Reported cases 1996–2003, n (%)	Risk category	Estimated risk
Transfusion-transmitted infection	45 (2.2)		
Post-transfusion purpura	44 (2.1)	Risk of serious hazard	1 in 11,000
Transfusion-associated GVHD	13 (0.6)	Risk of major morbidity	1 in 92,000
Unclassified	7 (0.3)	Risk of death	1 in 255,500

Prior to the introduction of ESAs, in addition to the immediate risks of transfusion reactions and infection, 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[263]. However, a subsequent assessment following the introduction of ciclosporin failed to confirm a benefit[262] and this subject remains controversial. Donor-specific transfusion prior to living-related transplantation appears favourable[116] 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 1 and 5 years[264]. 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[62]. 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[327]. Non-sensitised participants (PRA <10%) received a mean of 5.65 units (SEM 1.38), sensitised participants (PRA 11–59%) 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.

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 (Figure 7).

Figure 7: Recipient pre-transplant HLA-specific sensitisation: adult recipients of cadaver donor kidneys



(Manchester Kidney Transplants, NWKTA Audit Project, January 2003)

6.2.2 Methodological introduction

A comprehensive literature search identified two studies, a case-control study[77] and a before and after study[79].

Five studies[37,60,88,90,236,327] had methodological limitations and were therefore excluded from the evidence statements.

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

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)[77]. (Level 2+)

Dialysis patients

More patients in the lightly transfused group developed narrowly reactive antibodies (reacting with 10–29% panel cells) in comparison with 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 ($p<0.03$)[79]. (Level 3)

6.2.4 From evidence to recommendations

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 ciclosporin came into regular use. Ciclosporin improved survival, and taken together with the risk of the transmission of blood borne viruses and the availability of erythropoietin for treating anaemia, deliberate transfusion was discontinued.

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[79] was more clinically relevant than the data on the levels of different subtypes of lymphocytes induced by transfusion[77]. It was noted that 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.

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 (eg in some elderly patients). The GDG agreed that there were general clinical reasons to avoid blood transfusion and the relevant haematology guidelines should be followed (eg the British Committee for Standards in Haematology (BCSH) guidelines www.bcshguidelines.com).

6.2.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.3 Comparison of ESAs [2006]

6.3.1 Clinical introduction

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 three licensed forms of ESA currently available in England and Wales[c], two short-acting (epoetin alfa and epoetin beta) and one long-acting (Darbepoetin alfa).

Epoetin alfa 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. Epoetin alfa 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.

In both patients and normal volunteers, after intravenous administration of epoetin alfa, serum levels decline in a monoexponential manner and the volume of distribution is similar to that of the plasma volume. The half-life in normal volunteers is approximately 5 hours, but in patients with renal failure it is prolonged to approximately 9 hours. With multiple injections of epoetin alfa, half-life and clearance decrease. Measurement of epoetin alfa 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. After s.c. administration of epoetin alfa, peak serum levels occur between 12 and 18 hours later. The peak is always well below the peak achieved using the i.v. route (approximately 1/20th of the value). The bioavailability of subcutaneous injectable epoetin alfa is approximately 20% lower than that of the intravenous drug. Elevated levels of epoetin alfa are found in the serum 48 hours after a subcutaneous dose, but not after an intravenous dose.

Epoetin beta 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 epoetin beta to uraemic patients, the protracted absorption results in a serum concentration plateau, whereby the maximum concentration is reached after an average of 12 to 28 hours. The terminal half-life is higher than after intravenous administration, with an average of 13 to 28 hours. The bioavailability of epoetin beta after subcutaneous administration is between 23 and 42% when compared with intravenous administration.

The biological efficacy of epoetin alfa and epoetin beta has been demonstrated in various animal models in vivo (normal and anaemic rats, polycythaemic mice). After administration of epoetin alfa and epoetin beta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well

[c] Epotein delta was granted marketing approval in March 2002 by EMEA and introduction into the UK market is pending. Prescribers should be aware of developments in the available products and should check the most recent Summaries of Product Characteristics.

as the Fe-incorporation rate. It has been shown in cell cultures of human bone marrow cells that epoetin alfa and epoetin beta stimulate erythropoiesis specifically and do not affect leucopoiesis.

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

Darbepoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and epoetin alfa and beta. Following subcutaneous 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 intravenous 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 subcutaneous administration in patients with renal failure peak concentrations occur at 34 hours (range: 24 to 72 hours). Following intravenous administration, the terminal half-life of darbepoetin is approximately three times longer than epoetin alfa. The bioavailability of darbepoetin in patients with renal failure after subcutaneous administration is 37% (range: 30% to 50%).

6.3.2 Clinical methodological introduction

Epoetin alfa vs epoetin beta

There were no studies comparing epoetin alfa and epoetin beta.

Darbepoetin vs epoetin alfa

One multisite RCT[257] comparing darbepoetin and epoetin alfa was identified. One study[202] was excluded because of methodological limitations.

Notable aspects of the evidence base were:

- Of the 28-week study duration[257] the first 20 weeks were a dose titration and stabilisation period.

Darbepoetin vs epoetin beta

A comprehensive literature search identified one open-label RCT comparing darbepoetin and epoetin beta[358].

Notable aspects of the evidence base were:

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

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 alfa

Haemodialysis patients

Efficacy

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 that no significant difference was observed between the two treatment groups[257]. (Level 1+)

No significant difference was observed for:

- haemoglobin variability assessed as variance in haemoglobin
- percentage values within the Hb target range
- percentage values within the therapeutic range and instability of Hb levels requiring a dose change within the two treatment groups[257]. (Level 1+)

Dose change from baseline to evaluation was similar for both treatment groups[257]. (Level 1+)

The number of patients with dose changes during the titration and evaluation periods was similar for both treatment groups[257]. (Level 1+)

Safety

The type and frequency of adverse events was similar in both treatment groups, with no antibody formation to either treatment detected[257]. (Level 2+)

Darbepoetin vs epoetin beta

Haemodialysis patients

Efficacy

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[358]. (Level 1+)

Dose

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 (95%CI 17–61 IU/kg/week, $p<0.001$)[358]. (Level 1+)

Blood pressure

Blood pressure did not change significantly in the course of the study in either treatment arm[358]. (Level 1+)

6.3.4 Health economics methodological introduction

Only one economic evaluation[229] was found that compared darbepoetin and epoetin alfa. However, this study had methodological limitations and therefore no evidence statements were made. [d]

6.3.5 From evidence to recommendations

The GDG agreed that the evidence statements from the multisite RCT support the summary that there is no difference between darbepoetin and epoetin alfa for the outcomes measured, in a selected group of patients who were stable[257].

Evidence statements on efficacy suggest that both darbepoetin and epoetin beta effectively maintain target haemoglobin levels. ESAs are made available to NHS trusts through a system of tendering for local supply contracts. Costs therefore vary between locations and over time. The recommendation below outlines the considerations in agreeing on a first choice ESA rather than specifying a particular agent for all patients. This is intended to allow flexibility for local units over the lifetime of the guideline while providing useful advice in selecting the best treatment for the patient.

6.3.6 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.4 Early or deferred ESA therapy [2006]

6.4.1 Clinical introduction

The patients most likely to derive the greatest long-term benefit from correction of anaemia are those with chronic kidney disease who are predialysis. 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

A comprehensive literature search identified two studies[138,304].

Notable aspects of the evidence base were:

- One study[138] 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[138] was 13 g/dl, however, the mean Hb levels achieved was 12.9 g/dl (standard deviation 0.4) in the early treatment group and 10.3 g/dl (standard deviation 1.0) in the deferred treatment group.
- The target Hb levels for the other study[304] were 12–13 g/dl in the early treatment group and 9–10 g/dl in the deferred treatment group, while mean levels achieved were 12.1 g/dl (standard deviation 1.4) and 10.8 g/dl (standard deviation 1.3) respectively.

[d] In interpreting economic evaluation of ESAs, it should be borne in mind that different units will have developed their own pricing structures which may differ considerably from BNF list prices.

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

Left ventricular mass index

Predialysis patients

No significant differences were observed in left ventricular mass index measurements in a 2-year study[304] conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80) using epoetin. Treatment was 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. (Level 1++)

Renal function

Predialysis patients

No significant differences were observed in renal function (eGFR) in a 2-year study[304] conducted to maintain Hb 12–13 g/dl (n=75) vs 9–10 g/dl (n=80) using epoetin. However, eGFR progressively decreased in the two treatment arms (p<0.001). Treatment was 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. (Level 1++)

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[138]. (Level 1+)

Hypertension

Predialysis patients

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 systolic and diastolic blood pressure[304]. (Level 1++)

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 between the 2 treatment arms[138]. (Level 1+)

Quality of life

Predialysis patients

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 quality of life domains, as assessed by the Renal Quality of Life Profile and Short Form 36 (SF 36) questionnaires[304]. (Level 1++)

6.4.4 From evidence to recommendations

Both studies presented in the evidence were considered to be methodologically sound. The GDG felt that the study by Gouva et al[138] 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[304] 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.

The GDG felt they could not make any recommendations on this area based on these studies alone. The evidence showed no contraindication to early correction of anaemia.

6.5 Coordinating care [2006]

6.5.1 Clinical introduction

During the past decade in the UK, the management of anaemia associated with CKD has evolved into a nurse-led programme in many renal units. The introduction of specialist nurses dedicated to managing anaemia in CKD is in response to an increased number of patients receiving treatment for renal anaemia. 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 inefficient use of ESAs, 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.

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. For example, they may be responsible for a small case load such as haemodialysis patients and 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

A comprehensive literature search identified a before and after study[38]. However, because of methodological limitations, it was excluded from the evidence statements.

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

The GDG felt that there is a benefit to having a healthcare 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, for example nurses or pharmacists. The cost effectiveness varies according to the activity of the anaemia coordinator and improves with increasingly independent activity.

6.5.4 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.6 Providing ESAs [2006]

6.6.1 Clinical introduction

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 therapy 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

A comprehensive literature search identified one cross-sectional study[24].

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

6.6.3 Evidence statements

Predialysis, hospital and home haemodialysis and continuous ambulatory peritoneal dialysis patients

In a cross-sectional study[24] of 87 patients, ESA supply was found to be mostly by GPs (71%), followed by hospital pharmacies (29%), although 20 patients (23%) reported that their GPs had refused to supply an ESA. Of 124 patients, 51% preferred obtaining their ESA supplies from a community pharmacy, while 19% preferred a hospital pharmacy. The 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 provision of a larger supply (6%).

6.6.4 From evidence to recommendations

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 obtained from a source that took the patients choice and lifestyle into consideration.

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 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.7 ESAs: optimal route of administration [2006]

6.7.1 Clinical introduction

Three ESAs are currently available in the UK, two short-acting (epoetin alfa and epoetin beta) and one long-acting (darbepoetin). Short-acting ESAs are more suited to short dose intervals and long-acting ESAs are more suited to dosing intervals of at least a week or more. Intravenous administration of ESAs obviously requires intravenous access and is therefore logistically difficult in predialysis, peritoneal dialysis, and transplant patients. Patients on haemodialysis treatment may therefore easily receive ESA therapy 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

A literature search identified 58 studies. Because of 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 47: Studies included in the evidence statements

Route of administration	**Study type**
86	RCT
157	RCT, cross-over
157	RCT
182	RCT
190	RCT, cross-over
232	RCT
368	RCT
Frequency of administration	**Study type**
124	RCT
203	RCT
266	RCT
Patient population	**Study type**
99	Non-randomised study
183	Cohort study
267	Cohort study
Hypertension	**Study type**
249	Prospective longitudinal study
Patient preference	**Study type**
122	Prospective cross-sectional cross-over study

Four studies[152,217,238,333] were excluded from the evidence statements because of methodological limitations. The buffer used in the preparation in the patient preference study is no longer used, and the paper was therefore not considered further.

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.

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

6.7.3 Evidence statements

Haematocrit and arterial pressure

Haemodialysis patients

A 6-month study[249] conducted in hypertensive patients (n=13) found no significant changes in Hct after conversion of epoetin administration from the intravenous route to the subcutaneous route. However, a significant decrease in predialysis mean arterial pressure from the first month was observed ($p<0.05$). (Level 3)

Antihypertensive dose requirement

Continuous ambulatory peritoneal dialysis patients

In a 16-week RCT[182], a mean epoetin dose of 84 ± 9 U/kg/week administered subcutaneously vs a mean dose of 133 ± 7 U/kg/week administered intraperitonealy increased antihypertensive therapy in both groups, but no significant difference was found between the two groups. (Level 1+)

Pain

Haemodialysis patients

In an RCT study[122] (n=208) comparing intravenous and subcutaneous routes for three times weekly treatment[157], level of discomfort assessed using the Visual Analogue Scale found similar scores between the two modes of administration. (Level 1++)

ESA dose requirement

Haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients

In a 130-day non-randomised study investigating epoetin administration by subcutaneous vs intravenous routes (n=29)[99], 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 with 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 subcutaneous groups ($p<0.05$) when compared with the intravenously treated HD group. There were no differences in epoetin dose requirement between the subcutaneously 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[267]

comparing epoetin administration by the subcutaneous route in CAPD (n=8) vs HD (n=7) patients. (Level 2+)

In contrast to the above findings, a 24-week cohort study[183] comparing HD (n=10) vs CAPD (n=11) when epoetin was administered by the subcutaneous route found that the epoetin requirements, both to achieve and to maintain a target Hct of 30%, were higher in the HD group (both p<0.05). (Level 2+)

Frequency of administration

Haemodialysis patients

Three RCTs of 12–16 weeks duration[124,203,266] investigating subcutaneous epoetin administration once weekly vs twice weekly[203] and once weekly vs three times weekly[124,266], found no significant difference in epoetin requirement or rise in Hb levels[124,203] or systolic blood pressure in both groups[124]. (Level 1+)

Efficacy

Haemodialysis patients

Four RCTs of the following durations:

- 12 months[86]
- 8 to 24-week active treatment duration with 24-week follow-up period[232]
- 48-week duration consisting of a 26-week maintenance phase[157]
- 4-months[368]

compared subcutaneous vs intravenous epoetin administration three times weekly and found no significant differences in Hb/Hct levels between the two groups[86,169,232,368], although time to reach the target Hb was higher in the intravenously treated group (p=0.037) of one study[232].

One study[86] found no significant differences between the two modes of administration of epoetin in terms of the weight-standardised epoetin doses at monthly intervals or the cumulative epoetin dose to achieve target Hct 28–36%. One other study[232] found greater epoetin requirement in the intravenous group (p=0.019) during the Hb stabilisation (correction) phase of the study, but once target Hb was achieved in both groups, no difference was observed. Two other studies[157,368] found that the epoetin requirement was less for the subcutaneously treated group (p=0.02).

In addition, one study[232] assessed quality of life using the Kidney Disease Questionnaire and showed improvement in the physical and fatigue domains of both the intravenous and subcutaneous groups. These improvements, however, did not differ between the two routes of administration at any time. (Level 1+ and 1++)

In contrast to the above findings, in a randomised cross-over study[190] patients received similar doses of subcutaneous epoetin once (A1), twice (A2) or three times (A3) weekly (n=43), and crossed over to receiving intravenous epoetin once (B1), twice (B2) or three times (B3) weekly (n=38) over 3 months (or vice versa). A significant rise (p<0.001) in Hb was noted during the subcutaneous phase, whereas the intravenous phase was associated with a fall in Hb (p<0.001). (Level 1++)

Continuous ambulatory peritoneal dialysis (CAPD) patients

In a 16-week RCT (n=19), subcutaneously administered epoetin produced a rise in Hb levels (p<0.01), whereas intraperitonealy administered epoetin did not, despite a higher mean[182]. (Level 1+)

Peritoneal dialysis patients

Similarly to the CAPD patients, in a 32-week randomised cross-over study (n=13)[157] Hb levels in patients receiving intraperitoneal epoetin fell (p=0.03) when compared with the subcutaneous route. In support of this finding, the 16-week area under the Hct response curve (p=0.001) and the mean slope of the 16-week Hct response curve (p=0.05) were greater for subcutaneous dosing. Conversely, epoetin requirement per week was greater with intraperitoneal treatment in terms of 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). In addition, the mean total dose per week over the entire study was greater for the intraperitoneal route (p<0.01). (Level 1+)

6.7.4 Health economics: cost-minimisation analysis

A meta-analysis of trial data was conducted to compare costs for subcutaneous and intravenous administration of ESAs. Only epoetin beta had sufficient data to allow a valid comparison. Subcutaneous administration appears to save £1,100 ± £727 per patient per year, compared with intravenous administration. Full details are given in Appendix X.

6.7.5 From evidence to recommendations

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.

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 intravenous 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 subcutaneous route using short-acting ESAs required up to 30% less drug to be administered to achieve the same Hb/Hct.

6.7.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.8 ESAs: dose and frequency [2006]

6.8.1 Clinical introduction

Currently, the available ESAs fall into two 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.

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, the early days of ESA therapy showed that very rapid correction of anaemia was associated with significant adverse

effects. 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

A literature search identified nine studies[16,23,27,33,36,44,71,82,103].

Two studies[43,369] had methodological limitations and were therefore excluded from the evidence statements. As the meta-analysis[43] addressing route of administration had methodological limitations, the 10 studies within it were individually appraised and five met quality criteria[86,169,232,275,368]. The clinically relevant factors and respective study types are detailed in Table 48.

Table 48: Summary of included studies

Route of administration	Study design
Studies included in the meta-analysis	
[232]	RCT
[86]	RCT
[157]	RCT
[368]	RCT
[275]	Cohort study
Study published after the meta-analysis literature search cut-off date	
[36]	Cohort study
Starting Hb level	**Study design**
[33]	Prospective longitudinal study
Hypertension	**Study design**
[23]	Before and after study
[71]	RCT (open-label)
Rate of Hb correction	**Study design**
[16]	Prospective longitudinal study
[27]	Retrospective longitudinal study
[44]	Cohort study
[82]	Prospective longitudinal study
[103]	RCT(open-label)

The GDG agreed that the outcomes of priority were Hb levels, rate of Hb correction and complications.

Notable aspects of the evidence base were:

- Due to methodological limitations, one RCT[71] was downgraded to Level 2 in the evidence hierarchy.
- Adjuvant red blood cell transfusions were administered in addition to epoetin during the study period in four studies[33,82,103,157].
- Two studies addressing rate of Hb correction[27,82] were conducted in children.

6.8.3 Evidence statements

Route of administration

Table 49: Haemodialysis patients

Study reference	Evidence hierarchy	ESA therapy arms	Outcome
[36]	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 with 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.
[157]	Level 1++	Three times weekly i.v. vs three times weekly s.c.	Hb and Hct were similar in both groups. Average weekly epoetin dose was lower ($p=0.002$) in the s.c. group.
[368]	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 (ie >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).
[275]	Level 2+	s.c. vs i.v.	Hct levels were similar over the entire study period.
[86]	Level 1+	Three times weekly s.c. vs three times weekly i.v.	Weight-standardised epoetin doses at monthly intervals and cumulative epoetin doses were similar in both groups. Hct levels were similar in both groups.
[232]	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.

A meta-analysis of the four Level 1 studies addressing epoetin dose when administered s.c. vs i.v[86,169,232,368] found a lower epoetin requirement when administered s.c. (weighted mean difference (WMD) −30.05 (95% CI −43.96 to −16.14) I2 =7%). This was in support of the findings of the excluded heterogeneous meta-analysis[43]. A sensitivity analysis excluding the study with sample size n <20[86]

was also in agreement with this finding and ruled out heterogeneity (WMD −41.61 (95% CI −60.66 to −22.55) I2 =0%).

Table 50: Starting Hb level

Study reference	Patient population	Evidence hierarchy	Hb level at baseline	Outcome
[33]	Continuous ambulatory peritoneal dialysis (CAPD)	Level 3	≤7.5 g/dl vs >7.5 g/dl	Time to achieve Hb target was longer (p<0.001) in the lower Hb group at 6 months despite similar rate of Hb increase and epoetin dose in both groups.
[82]	Children on haemodialysis	Level 3 vs ≥6.8 g/dl	<6.8 g/dl	A similar proportion of each group (81% vs 80%) reached the 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).

Table 51: Hypertension: haemodialysis patients

Study reference	Evidence hierarchy	ESA therapy arms	Outcome
[23]	Level 3	i.v. three times weekly	No change in mean systolic and diastolic blood pressures was found, and only three of 24 patients who had required treatment for hypertension before epoetin therapy required an increased dose of antihypertensive medication.
[71]	Level 2+	Hct 40.8 ± 5.2% vs Hct 30 ± 4.3%	No differences were found in mean daytime systolic or diastolic BP and mean night time systolic or diastolic BP between the two groups.

Table 52: Rate of Hb correction

Study reference	Patient population	Evidence hierarchy	ESA therapy	Outcome
[16]	Predialysis	Level 3	s.c. twice weekly	There was a rise in Hb and Hct when compared with baseline levels after 3 months, which was sustained after 6 months and 12 months (all p<0.001). Target Hb was achieved 10–11 g/dl after 6 months.
[82]	Children on	Level 3	i.v. two to three	A median time to target of 11

Study reference	Patient population	Evidence hierarchy	ESA therapy	Outcome
	haemodialysis		times weekly with an aim to achieve a rise in Hb of 1 g/dl per 4 weeks in order to attain target Hb 9.6–11.2 g/dl	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).
[44]	Haemodialysis	Level 2+	Same weekly epoetin alfa dose in varying dose intervals	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 >11 g/dl throughout the 24-week study period.
[103]	Peritoneal dialysis patients	Level 1+	5, 10 and 20 U/kg epoetin daily s.c., to target Hct 30–35%	The differences in the mean weekly change in Hct were significant (p<0.05) over the 8 week constant-dose phase, between all three groups, in ascending order. 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 1,494, 1,523 and 1,678 U/kg respectively.
[27]	Post- transplant paediatric patients with chronic allograft dysfunction	Level 3	Thrice weekly s.c. vs twice weekly s.c. vs once weekly s.c.	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. Hct increase and epoetin starting dose were linearly related (r=0.44, p<0.05).

6.8.4 Health economics methodological introduction

One study[87] was identified in a literature search. Three studies[43,212,225] did not meet quality criteria. The included study[87] estimated the increased costs of changing from s.c. epoetin to i.v. epoetin in a retrospective analysis of 99 haemodialysis patients over 7 months.

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 X.3

6.8.5 Evidence statements

The mean dose in the 's.c. switched to i.v.' patients increased significantly (46.83 + 10.20 IU/kg/week, +34.9%, p=0.001) over 7 months and was estimated to increase costs by €1,841 + €401 (Euros, 2002) per patient per year (+26.3%)[87].

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

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.

An acceptable rate of rise of haemoglobin was considered to be ~1–2g/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.

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.

The included health economic study supported the excluded meta-analysis[43] that intravenous administration of short-acting ESAs was more costly than subcutaneous administration.

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

6.8.7 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.9 Optimal Hb levels [2006]

6.9.1 Clinical introduction [2011]

Much of the published research in the treatment of CKD-related anaemia in the last decade has focused upon the optimum range of Hb to which patients should be treated. The prevailing research question has been 'since lower Hb is consistently associated with poor outcomes, does raising Hb to more normal levels improve outcomes?' The four largest randomised controlled trials in anaemia management in CKD that have attempted to answer this (US Normalization of Hematocrit trial[41], CREATE[96], CHOIR[322] and TREAT[279]) have generated debate and controversy in the literature. Most would at least agree that Hb is a biomarker and indeed the achieved Hb in RCTs was not related to the clinical consequences[41,341], which has raised the question of Dose Targeting Bias[271] in these studies.

The Hb achieved by any given patient is a composite of patient-related factors and co-morbidities, intercurrent events and clinical management (Table 53). The time taken to achieve any desirable Hb target range is dependent on all of these, the baseline Hb level and an individual patient's responsiveness to anaemia therapy. Even in well conducted RCTs designed to achieve similar Hb ranges, where care is taken to control for as many of these factors as possible, we observe considerable variation in what can be achieved, and what it takes to do this.

Although Hb level is the quantitative measure of anaemia, the optimal treatment of renal anaemia demands consideration of what clinical results we are anticipating, and how we are going to produce them, rather than focussing only on a Hb level within a given range. Erythropoiesis stimulating agents (ESAs) have major effects on the bone marrow and red blood cell survival , but erythropoietin receptors are found also in the brain, retina, heart, skeletal muscle, kidney and endothelial cells[306]. EPO-receptor activation plays a role in cell differentiation, proliferation and apoptosis through a variety of signalling pathways and it has been suggested that high treatment doses of ESAs may be related causally to the adverse effects reported in recent randomised controlled trials[321].

In making guideline recommendations for desirable treatment ranges we need to consider patient-related outcomes (mortality, cardiovascular and renal outcomes, safety, quality of life, and transfusions) together with Hb level and ESA dose. We should keep in mind that guideline recommendations form a background to the clinical assessment of benefits and risk for individual patients.

Table 53: Factors contributing to Hb variability

Patient factors and co-morbidities	Intercurrent events	Practice pattern-related
Red cell lifespan	Infection & transient inflammation	ESA dose adjustment protocol design
Chronic inflammation	Hospitalization	Iron therapy protocol
Patient adherence	Iron deficiency	Protocol compliance
Secondary hyperparathyroidism	Bleeding/haemolysis	Laboratory monitoring
Chronic viral infection	Malnutrition	Narrow target Hb range
Malignancies	Vitamin deficiency	Dialysis adequacy
Haematological disorders	Pure red cell aplasia	Water purity
Complications of diabetes	Medications eg. ACE inhibitors	Payment restrictions
Other	Interdialytic weight gain	

Reprinted from: Stevens 2008[336] (This table is reproduced with permission from Dr Anatole Besarab)

The GDG agreed to address the following question: *what should be the aspirational Hb (Hb) target range for patients undergoing treatment for anaemia in CKD?*

6.9.2 Clinical methodological introduction

A literature search identified one meta-analysis[338] containing 19 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) (seven 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).

An additional three RCTs[219,220,272] and a prospective longitudinal study[121] were found which addressed the effects of lower vs higher Hb levels.

The different Hb levels examined and study durations need to be accounted for when evaluating the evidence and are summarised in Table 54.

Table 54: Study duration and Hb levels for the included studies

Reference	Study duration	Low Hb (g/dl)	High Hb (g/dl)
[338]	6 to 29 months	9.0–12.0	11.9–15.0
[338]	2 to 12 months	7.5–10.4	9.5–13.3
[219]	8 months	9.0	12.0
[272]	24 months	10.9 ± 0.7	12.6 ± 1.0
[121]	8 months	10.5 ± 0.9	12.6 ± 1.0

Notable aspects of the evidence base were:

- Although the meta-analysis[338] was of rigorous methodology leading to a systematic review of a high standard, the trials within it were of variable quality.
- The meta-analysis[338] was heavily weighted by a single study[41] 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[338] enrolled children, the findings were not stratified on the basis of age.
- Due to methodology limitations, one RCT[219] 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.

Clinical methodological introduction [2011]

A literature search was undertaken to retrieve papers published from 2005 onwards for RCTs considering the aspirational Hb target range for people with anaemia in CKD. Twelve reports of eight RCTs[96,98,117,192,218,272,279,301,307,322,341,342] were identified. Systematic reviews [129,153,268,273,281,338,339] identified in the searches were cross-checked to ensure all relevant trials had been identified and included in the review.

For studies with an adult population, RCTs were included if there were at least 100 patients randomised and compared two target Hb levels. For studies in the paediatric population all RCTs,

irrespective of sample size were considered for inclusion. In addition, studies examining treatment targets and drug versus placebo comparisons were included.

Results for adults and children as well as the non-dialysis and dialysis populations are presented separately.

16 reports of 12 RCTs (identified from the old guideline and update searches) with varying degrees of bias were found which addressed the question and were included in the review.

The characteristics of the included studies are reported in Appendix BB. Notable aspects of the evidence base were:

- 11 reports of 8 RCTs[96,98,192,208,279,301,304,307,322,341,342] included patients with non-dialysis CKD, and 4 reports of 3 RCTs[41,117,118,272] were in dialysis patients and one study[128] included both groups [results are reported separately].
- Non-dialysis dependent CKD trials stated the inclusion criteria with respect to mean GFR of ≤60 mL/min. One study[192] included patients with creatinine clearance levels between 15 to 79 mL/min.
- The baseline aspirational and achieved Hb levels for the included studies are summarised in Table 55 and Figure 8 (Paragraph 6.9.5).
- Patients were administered epoetin-alfa[41,118,128,192 208,272,304,307,322], epoetin-beta[96 301,307] or darbepoetin[279]. Details on dosage and mode of administration are described in Figure 9 and Figure 10.

Table 55: Baseline, target and achieved Hb levels for non-dialysis and dialysis populations

Study	High target				Low target		
	High target Hb (g/dL)				Low target Hb (g/dL)		
	Baseline	Target	Achieved		Baseline	Target	Achieved
Non-dialysis							
ACORD[301]	11.9 (IQR 11.3 to 12.2)	13 to 15	13.5		11.9 (IQR 11.3 to 12.0)	10.5 to 11.5	12.1
CREATE§[96]	11.6 (SD 0.6)	13 to 15	13.3 (SD 0.5)		11.6 (SD 0.6)	10.5 to 11.5	11.8 (SD 0.7)
CHOIR*[322]	10.1 (SD 0.9)	13.5	12.6		10.1 (SD 0.9)	11.5	11.3
TREAT¶[279]	10.5 (IQR 9.8 to 11.0)	13	12.5 (IQR 12.0-12.8)		10.4 (IQR 9.8 to 10.9)	>9	10.6 (IQR 9.9-11.3)
Furuland 2003[128]	10.6 (SD 1.0)	13.5 to 16	14.3 (SD 1.1)		10.9 (SD 0.7)	9 to 12	11.7 (SD 1.3)
Levin 2005[192]	11.76 (SD 0.76)	12 to 14	12.7 (SD 0.88)		11.73 (SD 0.80)	9 to 10.5	11.4 (SD 1.2)
Macdougall 2007†[208]	10.89 (SD 0.60)	10 to 12	11		10.76 (SD 0.66)	>9	10.48
Roger 2004[304]	11.2 (SD 0.9)	12 to 13	12.1 (SD 1.4)		11.2 (SD 0.8)	9 to 10	10.8 (SD 1.3)
Rossert 2006[307]	11.5 (SD 1.0)	13 to 15	13.5 (SD 1.9)		11.6 (SD 0.9)	11 to 12	11.9 (SD 1.6)
Dialysis							
Besarab 1998[41]	10.2 (SD 1.0)	13 to 15	13.2		10.2 (SD 1.0)	9 to 11	10
Foley 2000[118]	10.4 (95% CI 10.2 to 10.6)	13 to 14	12.2		12.2 (95% CI 11.9 to 12.5)	9.5 to 10.5	10.4
Furlund 2003[128]	HD: 11.0 (SD 1.1); PD: 11.2 (SD 0.9)	13.5 to 16	HD : 13.5(1.4); PD: 13.4 (1.5)		HD: 11.0 (SD 0. 9); PD: 11.2 (SD 0.9)	9 to 12	HD: 11.3 (SD 1.3); PD: 11.5 (SD 1.2)
Parfrey 2005‡[272]	11.0 (SD 1.2)	13.5 to 14.5	13.1 (SD 0.9)		11.0 (SD 1.2)	9.5 to 11.5	10.8 (SD 0.7)

§One secondary analysis[98] of the CREATE trial was identified. *Two secondary analyses[341,342] of the CHOIR trial were identified. One study reported results for diabetes and heart failure patients. However, the study did not report the mean Hb values for these groups. ‡One report[117] of the Parfrey (2005) study[272] was identified and included in the review.

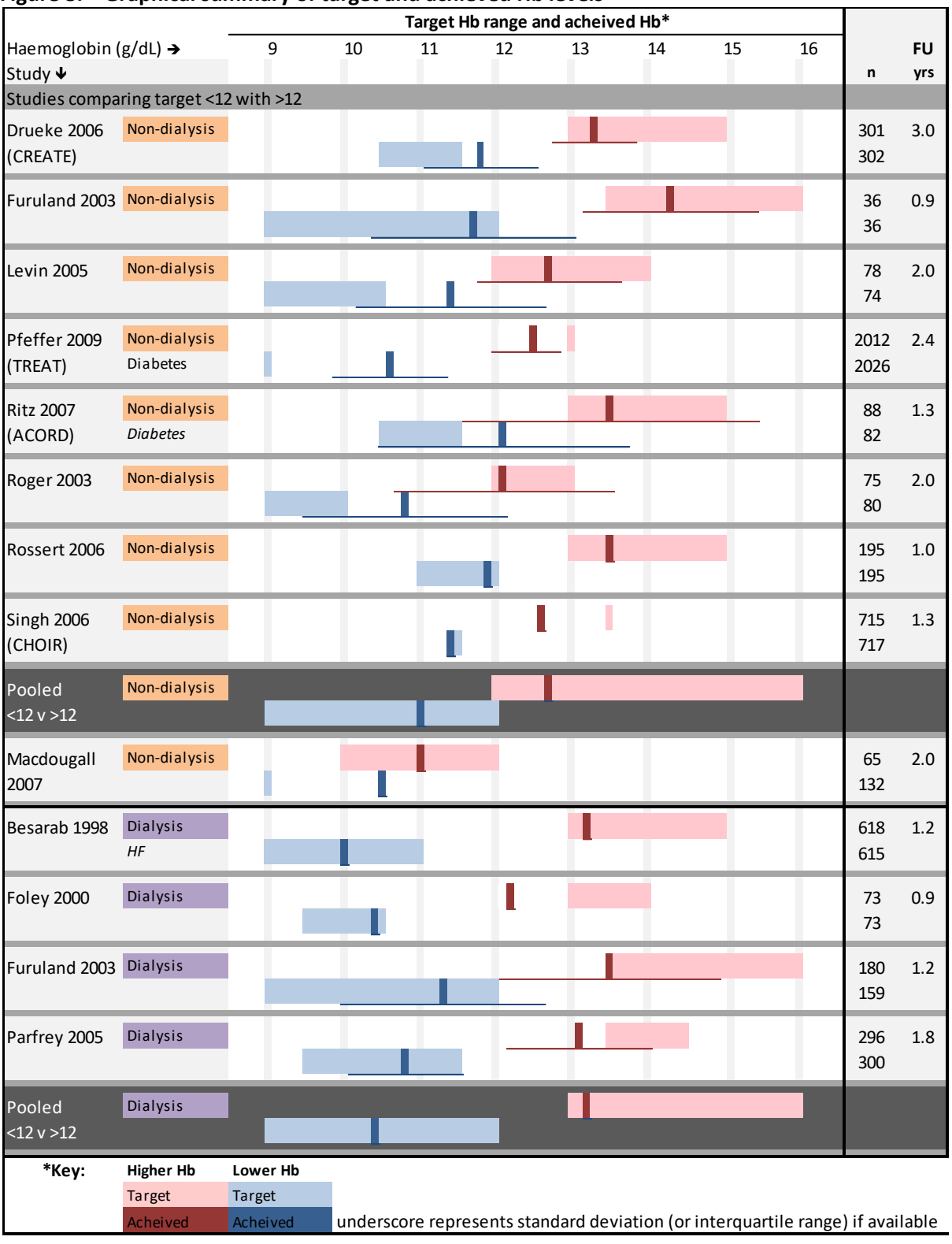
¶ TREAT: patients randomised to the placebo group were assigned to receive darbepoetin alfa as rescue therapy if the Hb level fell below 9.0 g/dL. Rescue therapy continued until the Hb level increased to ≥ 9.0 g/dL, at which time placebo administration resumed.

†Macdougall 2007[208]: treatment commenced when Hb had remained at ≤9.0 g/dL for 3 months or had fallen to ≤8.0 g/dL on two consecutive occasions 2 weeks apart or clinical symptoms of anaemia had developed.

Data are presented as mean (SD), median (IQR) or mean (95% CI).

HD= haemodialysis; PD=peritoneal dialysis

Figure 8: Graphical summary of target and achieved Hb levels



Evidence Profiles [2011]

The evidence profiles (Table 57 to Table 59) summarise the quality of the evidence and outcome data from the 15 reports of 12 RCTs included in this review, comparing two target Hb levels. Results are presented by outcomes for the non-dialysis and dialysis populations. The update work below presents the following evidence profile tables:

Table No	Population	Hb group
Table 57	Non-dialysis	>12.0 g/dL vs lower Hb
Table 58	Non-dialysis	10-12 g/dL vs lower Hb
Table 59	Dialysis	>12.0 g/dL vs lower Hb

6.9.3 Clinical evidence statements [2006, updated 2011]

Table 56: Summary of appraised studies

Reference	Outcome	Patient population (n)	Aiming for a high Hb	Aiming for a low Hb	Evidence grading
[338]	All-cause mortality	Predialysis, peritoneal dialysis and haemodialysis (n=1949)	11.9-15.0g/dl	9.0-12.0 g/dl ↓	Level 1++
[338]	All-cause mortality	Predialysis, peritoneal dialysis and haemodialysis (n=255)	9.5-13.3 g/dl	7.5-10.4 g/dl No difference	Level 1++
[338]	Hypertension	Predialysis, peritoneal dialysis and haemodialysis (n=1277)	11.9-15.0 g/dl	9.0-12.0 g/dl No difference	Level 1++
[220]	Hypertension	Haemodialysis (n=12)	12.0 g/dl ↑	9.0 g/dl	Level 2+
[338]	Quality of life	Predialysis, peritoneal dialysis and haemodialysis (n=unknown)	11.9-15.0 g/dl	9.0-12.0 g/dl No difference	Level 1++
[338]	Quality of life	Predialysis, peritoneal dialysis and haemodialysis (n= unknown)	9.5-13.3 g/dl	7.5-10.4 g/dl No difference	Level 1++
[219]	Quality of life	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference	Level 2+
[220]	Physical performance-exercise radionuclide ventriculogram	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference	Level 2+
[220]	Physical performance-	Haemodialysis (n=12)	12.0 g/dl ↑	9.0 g/dl	Level 2+

Reference	Outcome	Patient population (n)	Aiming for a high Hb	Aiming for a low Hb	Evidence grading
	maximal incremental exercise testing				
[272]	6-minute walking distance	Haemodialysis (n=596)	12.6±1.0 g/dl	10.9±0.7 g/dl No difference	Level 1++
[220]	Left ventricular mass and mass index	Haemodialysis (n=12)	12.0 g/dl	9.0 g/dl No difference (note: short study duration)	Level 2+
[272]	Left ventricular volume index left ventricular mass index	Haemodialysis (n=596)	12.6±1.0 g/dl	10.9±0.7 g/dl No difference in either cardiovascular parameter	Level 1++
[121]	Left ventricular septal, posterior wall thickness and left ventricular mass index. Left ventricular ESD and EDD RWT parameter for left ventricular geometry		13.4±3.1 g/dl All ↓ No difference ↓	10.5±0.9 g/dl	Level 3

↑= significant increase; ↓= significant decrease.

Table 57: Non-dialysis: >12g/dL versus lower Hb

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	>12g/dL compared to lower Hb levels-non dialysis	control	Relative (95% CI)	Absolute	Quality
All cause mortality > 12 g/dL v lower Hb level (follow-up 1-4 years) 13-16 v 9-12 [12.5-14.5 v 10.6-11.9]											
6	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	501/3338 (15%)	462/3349 (13.8%) 0%	HR 1.10 (0.97 to 1.24)	13 more per 1000 (from 4 fewer to 30 more) 0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW
CV mortality 13-16 v 9-12 [13.3-14.3 v 11.7-11.8]											
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/337 (4.5%)	10/338 (3%)	RR 1.5 (0.69 to 3.3)	15 more per 1000 (from 9 fewer to 68 more)	⊕OOO VERY LOW
Composite outcome (death, MI, hospitalisation for congestive heart failure) 13-15 v 9-11.55 [12.5-13.3 v 10.6-11.8]											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	815/3028 (26.9%)	746/3045 (24.5%)	HR 1.1 (1 to 1.21)	21 more per 1000 (from 0 more to 43 more)	⊕⊕⊕O MODERATE
Mean decrease in GFR 12-16 v 9-12 [12.1-14.3 v 10.6-11.9] (follow up 1-4 years) (Better indicated by lower values)											
5	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	539	546	-	SMD 0.04 lower (0.16 lower to	⊕⊕⊕O MODERATE

										0.07 higher)	
Change in creatinine clearance (mL/min) 12-14 v 9-10.5 [12.7 vs 11.4] (Better indicated by lower values)											
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[3]	none	78	74	-	MD 1.7 higher (1.66 lower to 5.06 higher)	⊕OOO VERY LOW
Initiation of dialysis 12-15 v 9-11.5 [12.1-13.5 v 10.8-12.1]											
4	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	164/541 (30.3%)	137/536 (25.6%)	RR 1.2 (1 to 1.44)	51 more per 1000 (from 0 more to 112 more)	⊕OOO VERY LOW
Worsening renal function 13-15 v 11-12 [13.5 v 11.9]											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/195 (1%)	2/195 (1%)	RR 1 (0.14 to 7.03)	0 fewer per 1000 (from 9 fewer to 62 more)	⊕OOO VERY LOW
Proportion of patients transfused 13-15 v >9-11.5 [12.5-13.3 v 10.6-11.8]											
2	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	323/2313 (14%)	529/2328 (22.7%)	RR 0.61 (0.54 to 0.7)	89 fewer per 1000 (from 68 fewer to 105 fewer)	⊕⊕⊕O MODERATE
Stroke (stroke included: TIA/stroke, neurological deficit not reversible w/in 24 hours) 13-15 v 9-11.5 [12.5-13.5 v 10.6-11.8]											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/3028 (4.2%)	72/3045 (2.4%)	HR 1.69 (1.28 to 2.24)	16 more per 1000 (from 7 more to 29 more)	⊕⊕⊕O MODERATE
MI 13-15 v 9-12 [12.5-13.5 v 10.6-11.9]											
4	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[3]	none	158/3223 (4.9%)	166/3240 (5.1%)	RR 0.88 (0.64 to 1.2)	6 fewer per 1000 (from 18 fewer to 10 more)	⊕OOO VERY LOW

Hypertension (definition varied: BP>160mm Hg; at least 1 recorded BP>140/90mm Hg) 12-15 v 9-12 [12.5-13.5 v 10.6-12.1]											
5	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	none	663/2674 (24.8%)	574/2679 (21.4%)	RR 1.16 (1.05 to 1.27)	34 more per 1000 (from 11 more to 58 more)	⊕⊕OO LOW
Change in LVMI [g/m2]- (follow-up 1.25 to 2 years) 12-15 v 9-11.5 [12.1-13.5 v 10.8-12.1] (Better indicated by lower values)											
4	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[3]	none	542	538	-	MD 1.08 lower (4.45 lower to 2.29 higher)	⊕OOO VERY LOW
Change in LVMI [g/m2]- (1 year) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	171	186	-	MD 2.00 lower (7.19 lower to 3.19 higher)	⊕⊕⊕O MODERATE
Change in LVMI [g/m2]- (2 years) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[13]	none	136	146	-	not pooled	⊕⊕OO LOW
Change in LVMI[g/m2] - (3 years) (Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	81	-	MD 6.20 higher (4.19 lower to 17.31 higher)	⊕⊕⊕O MODERATE
CV event free survival – Concentric LVH (1 year)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	38/43 (88.4%)	35/42 (83.3%)	RR 1.06 (0.89 to 1.26)	50 more per 1000 (from 92 fewer to 217 more)	⊕OOO VERY LOW
CV event free survival– Concentric LVH (2 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											

1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	33/43 (76.7%)	29/42 (69%)	RR 1.11 (0.86 to 1.44)	76 more per 1000 (from 97 fewer to 304 more)	⊕OOO VERY LOW
CV event free survival– Concentric LVH (3 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/43 (37.2%)	18/42 (42.9%)	RR 0.87 (0.52 to 1.46)	56 fewer per 1000 (from 206 fewer to 197 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (3 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/61 (26.2%)	28/66 (42.4%)	RR 0.62 (0.37 to 1.03)	161 fewer per 1000 (from 267 fewer to 13 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (1 year) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	50/61 (82%)	61/66 (92.4%)	RR 0.89 (0.77 to 1.02)	102 fewer per 1000 (from 213 fewer to 18 more)	⊕OOO VERY LOW
CV event free survival – Eccentric LVH (2 years) 13-15 v 10.5-11.5 [13.3 v 11.8]											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[3]	none	33/61 (54.1%)	46/66 (69.7%)	RR 0.78 (0.59 to 1.03)	153 fewer per 1000 (from 286 fewer to 21 more)	⊕OOO VERY LOW
Change in SF-36: physical function 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
4	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	3118	3142	-	MD 0.40 higher (0.17 lower to 0.97 higher)	⊕OOO VERY LOW
physical role 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											

3	randomised trials	serious[18]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.19 higher (1.82 lower to 2.21 higher)	⊕OOO VERY LOW
pain 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.19 lower (2.32 lower to 1.93 higher)	⊕OOO VERY LOW
general health 13-15 v 10.5-12 [12.6-13.5 v 11.3-12.1] (Better indicated by lower values)											
4	randomised trials	serious[19]	no serious inconsistency	no serious indirectness	serious[13]	none	1192	1198	-	MD 3.96 higher (1.72 to 6.2 higher)	⊕⊕OO LOW
vitality 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
4	randomised trials	serious[16]	serious[17]	no serious indirectness	serious[13]	none	3318	3142	-	MD 0.88 higher (0.15 to 1.6 higher)	⊕⊕OO LOW
social function - 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.91 higher (1.26 lower to 3.08 higher)	⊕OOO VERY LOW
emotional role 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											
3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 1.70 lower (4.84 lower to 1.44 higher)	⊕OOO VERY LOW
mental health 13-15 v 10.5-12 [12.6-13.5 v 11.3-11.9] (Better indicated by lower values)											

3	randomised trials	serious[16]	serious[17]	no serious indirectness	very serious[3]	none	1104	1116	-	MD 0.44 higher (0.73 lower to 1.61 higher)	⊕OOO VERY LOW
physical health composite score 12-13 v 9-10 [12.1 v 10.8] (Better indicated by lower values)											
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	very serious[3]	none	75	80	-	MD 1.00 lower (5.26 lower to 3.26 higher)	⊕OOO VERY LOW
mental health composite score 12-13 v 9-10 [12.1 v 10.8] (Better indicated by lower values)											
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	very serious[3]	none	75	80	-	MD 3.00 higher (0.98 lower to 6.98 higher)	⊕OOO VERY LOW

[1] Studies: CHOIR, CREATE, TREAT, Furuland 2006, Levin 2005, Rossert 2006: 4/6 had unclear allocation concealment, 2/6 blinding not done; 1/6 blinding unclear; 3/6 open label trial; Three trials were powered for composite outcomes not for all-cause mortality; CHOIR and Rossert trials terminated early

[2] Moderate heterogeneity (I2=47%; p=0.09)

[3] 95% CI includes both the line of appreciable benefit and harm

[4] CREATE, Furuland 2006: unclear allocation concealment and blinding

[5] CHOIR, CREATE, TREAT: 2/3 unclear allocation concealment; 2/3 no blinding; 1/3 unclear blinding. CHOIR terminated early

[6] CREATE, Furuland 2006, Levin 2005, Roger 2004, Rossert 2006: 4/5 unclear allocation concealment; 4/5 open label; 1/5 unclear blinding. Rossert terminated early

[7] Levin 2005: open label

[8] ACORD, CREATE, Levin 2005, Roger 2004:3/4 unclear allocation concealment; 1/4:unclear blinding;3/4 blinding not done

[9] Rossert 2006- unclear allocation concealment and not blinded. Rossert terminated early

[10] CREATE, TREAT- 2/2 unclear allocation concealment; blinding unclear

[11] CREATE, CHOIR, TREAT, Rossert 2005: 4/4 unclear allocation concealment ; 1/4: unclear blinding and 3/4 not blinded

[12] ACORD, CREATE, TREAT, Levin 2005, Rossert 2006: 4/5 unclear allocation concealment; unclear if blinded/not blinded. Rossert terminated early

[13] 95% CI includes appreciable benefit/harm

[14] ACORD, CREATE, Levin 2005, Roger 2004: 3/4 unclear allocation concealment and 3/4 blinding unclear 1/4 blinding not done

[15] Eckardt 2009: secondary analysis of CREATE; results reported for patients who had echocardiogram available at baseline and at 1, 2 and 3 years

[16] CREATE, CHOIR, TREAT, Rossert 2006:3/4 unclear allocation concealment; 1/4 blinding unclear, 1/4 open label blinded and 2/4 blinding not done; CHOIR and Rossert terminated early

[17] Significant heterogeneity

[18] CREATE, CHOIR, Rossert 2006:3/3 unclear allocation concealment; 1/3 open label;3/4 blinding unclear/not done; CHOIR and Rossert terminated early

[19] ACORD, CREATE, CHOIR, Rossert 2006: 4/4 unclear allocation concealment ;1/4 open label: 3/4 unclear or not blinded

[20] Roger 2006:unclear allocation concealment and not blinded

Results for the quality of life outcome reported in Table 57 includes unpublished data for two trials[155,302] . Data received upon request from the sponsors

Results for two studies[301,304] for progression of CKD are reported below in a narrative format as the studies either did not report the numerical values or were reported in a format that would not allow for analysis in RevMan or the GRADEpro programme.

One study[301] reported median (IQR) for decrease in eGFR (mL/min) [calculated using MDRD formula]: -5.1 mL/min (IQR -10.7 to -0.1) vs -3.9 mL/min (IQR -12.1 to 1.8) for the high (13-15 g/dL) and the low (10.5-11.5 g/dL) Hb target groups, respectively. It also reported median (IQR) for decrease in creatinine clearance (mL/min) [calculated using Cockcroft-Gault formula]: -5.5 mL/min (IQR -11.5 to -0.1) vs -3.4 mL/min (IQR -11.4 to 2.0) for the high (13-15 g/dL) and the low (10.5-11.5 g/dL) Hb target groups, respectively.

A second study[304] stated that creatinine clearance values would be reported but data was not shown. The study noted that calculated creatinine clearance values [Cockcroft-Gault formula] exhibited similar results to decrease in GFR.

Table 58: Non-dialysis: 10 to 12g/dL versus lower Hb levels

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	10-12 g/dL compared to lower Hb level in pre-dialysis patients	control	Relative (95% CI)	Absolute	Quality
All cause mortality - 10-12 v >9 [11 v 10.48];@21-24mo.											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/64 (1.6%)	5/132 (3.8%)	RR 0.41 (0.05 to 3.46)	22 fewer per 1000 (from 36 fewer to 93 more)	⊕OOO VERY LOW
Creatinine clearance [mL/min] - 10-12 v >9 [11 v 10.48] (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	132	-	MD 0.86 higher (1.55 lower to 3.27 higher)	⊕⊕⊕O MODERATE
Initiation of dialysis - 10-12 v >9 [11 v 10.48]											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/65 (44.6%)	61/132 (46.2%)	RR 0.97 (0.7 to 1.34)	14 fewer per 1000 (from 139 fewer to 157 more)	⊕OOO VERY LOW
Change in LVMI- 2 years - 10-12 v >9 [11 v 10.48] (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	111	-	MD 15.4 lower (39.69 lower to 8.89 higher)	⊕⊕⊕O MODERATE

Hypertension - 11 v >9 [11 v 10.48]											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/65 (21.5%)	9/132 (6.8%)	RR 3.16 (1.44 to 6.91)	147 more per 1000 (from 30 more to 403 more)	⊕⊕⊕O MODERATE

[1] Macdougall 2007; 1/1 had unclear allocation concealment and was open label trial
[2] 95% CI includes both the line of appreciable benefit and harm

Table 59: Dialysis: > 12 g/dL versus lower Hb

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	>12g/dL compared to lower Hb levels-dialysis	control	Relative (95% CI)	Absolute	Quality
All cause mortality (follow up 48-56 weeks) 13-16 V 9-12 [12.2-13.5 v 10-11.3]											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	223/871 (25.6%)	189/852 (22.2%)	RR 1.11 (0.88 to 1.4)	24 more per 1000 (from 27 fewer to 89 more)	⊕OOO VERY LOW
CV mortality 13-16 v 9-12 [13.1-13.5 v 10-11.3]											
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	159/1094 (14.5%)	147/1079 (13.6%)	RR 1.07 (0.87 to 1.31)	10 more per 1000 (from 18 fewer to 42 more)	⊕OOO VERY LOW
Access Thrombosis 13-16 v 9-11.5 [13.1-13.5 v 10-11.3]											
4	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	301/1144 (26.3%)	242/1124 (21.5%)	RR 1.24 (1.07 to 1.43)	52 more per 1000 (from 15 more to 93 more)	⊕OOO VERY LOW

Number of patients transfused 13-15 v 9-11.5 [13.1-13.2 v 10-10.8]											
2	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/914 (17.1%)	250/915 (27.3%)	RR 0.62 (0.52 to 0.74)	104 fewer per 1000 (from 71 fewer to 131 fewer)	⊕⊕⊕O MODERATE
MI 13-15 v 9-11.5 [13.1-13.2 v 10-10.8]											
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[2]	none	26/914 (2.8%)	18/915 (2%)	RR 1.44 (0.8 to 2.61)	9 more per 1000 (from 4 fewer to 32 more)	⊕OOO VERY LOW
Fatal MI 13-15 v 11-12 [13.2 v 10]											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	22/618 (3.6%)	28/615 (4.6%)	RR 0.78 (0.45 to 1.35)	10 fewer per 1000 (from 25 fewer to 16 more)	⊕OOO VERY LOW
Cardiac event 13-14 v 9.5-10.5 [12.2-10.4]											
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/73 (13.7%)	10/73 (13.7%)	RR 1 (0.44 to 2.26)	0 fewer per 1000 (from 77 fewer to 173 more)	⊕OOO VERY LOW
Hypertension - 13.5-14.5 V 9.5-11.5 [13.1 v10.8]											
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	120/296 (40.5%)	110/300 (36.7%)	RR 1.11 (0.9 to 1.35)	40 more per 1000 (from 37 fewer to 128 more)	⊕OOO VERY LOW
Change in LVMI 13.5-14.5 v 9.5-11.5 [13.1 v 10.8] (Better indicated by lower values)											
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	260	256	-	MD 2.6 lower (12.3 lower to 7.1 higher)	⊕OOO VERY LOW

Quality of life - Physical function (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	349	-	MD 0.13 lower (4 lower to 3.74 higher)	⊕⊕⊕O MODERATE
Quality of life - Physical role (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	349	-	MD 2.06 lower (8.96 lower to 4.84 higher)	⊕⊕⊕O MODERATE
Quality of life - Pain (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	350	-	MD 0.72 lower (5.23 lower to 3.79 higher)	⊕⊕⊕O MODERATE
Quality of life - General Health (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	317	351	-	MD 0.18 higher (2.95 lower to 3.31 higher)	⊕⊕⊕O MODERATE
Quality of life - Vitality (Better indicated by lower values)											
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	596	629	-	MD 3.05 higher (0.77 to 5.34 higher)	⊕⊕⊕O MODERATE
Quality of life - Social function (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316	350	-	MD 0.87 higher (3.85 lower to 5.59 higher)	⊕⊕⊕O MODERATE
Quality of life - Emotional role (Better indicated by lower values)											

1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	309	346	-	MD 3.23 higher (4.67 lower to 11.13 higher)	⊕⊕⊕O MODERATE
Quality of life - Mental health (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	314	348	-	MD 0.43 lower (3.34 lower to 2.48 higher)	⊕⊕⊕O MODERATE
Quality of life - Mental health composite score (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	312	347	-	MD 0.89 higher (0.92 lower to 2.7 higher)	⊕⊕⊕O MODERATE
Quality of life - Physical health composite score (Better indicated by lower values)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	347	-	MD 0.43 lower (1.85 lower to 0.99 higher)	⊕⊕⊕O MODERATE

1 Besarab 1998, Foley 2000, Furuland 2003: 3/3unclear allocation concealment; 3/3 open label trials. Besarab trial terminated early.
2 95% CI include both the line of appreciable benefit and harm
3 Besarab 1998;Furuland 2003;Parfrey 2005: 3/3unclear allocation concealment; 2/3 not blinded and unclear in one study. Besarab trial terminated early.
4 Besarab 1998; Foley 2000; Furuland 2003; Parfrey 2005: all- unclear allocation concealment; 2/4 open label and 1/4 blinding unclear; Besarab trial terminated early
5 Significant heterogeneity: I2=63% p=0.04
6 95% confidence interval includes appreciable benefit or harm
7 Besarab 1998; Foley 2008: 1/2 unclear allocation concealment; 1/2 open label; Besarab trial terminated early
8 Besarab 1998; Parfrey 2005; 2/2 unclear allocation concealment;1/2 open label; 1/2 unclear blinding
9 Besarab 1998; unclear allocation concealment; open label; Besarab trial terminated early.
10 Foley 2000: unclear allocation concealment; open label
11 Parfrey 2005: unclear allocation concealment and blinding
12

Results for the quality of life outcome reported in Table 59 include unpublished data from one trial[20]. Data received upon request from the sponsor.

One study[118] reported that the change in LVMI was similar for both Hb target groups but the numerical values were not reported. The study noted there was no correlation between the mean Hb level and the observed echocardiographic change.

Clinical evidence statements [2011]

The evidence statements are grouped by comparisons (>12 g/dL versus lower Hb; 10 to 12 g/dL versus lower Hb) and results are given for non-dialysis and dialysis populations.

Table 60 to Table 62 are presented here to provide a brief overview of the results.

Table 60: Increased risk/benefit for high/low Hb in NON-DIALYSIS patients: Comparison: >12 g/dL versus lower Hb; [The aspirational Hb levels are noted within the square brackets]

	High Hb target g/dL	Low Hb target
Increased risk in the higher Hb group for :	Composite events*‡ [13-15 vs >9-11.5]	
	Stroke [13-15 vs >9-11.5]	
	Hypertension [12-15 vs 9-12]	
	Initiation of dialysis‡ [12-15 vs 9-11.5]	
	Worse CV event free survival (in patients with eccentric LVH at baseline) [13-15 vs 10.5-12.5]	
No difference	• Mortality • CV mortality • MI • Progression of CKD [mean decrease in GFR; creatinine clearance] • Change in LVMI • QoL (physical function, physical role, pain, role –emotional, social function, mental health, physical health composite score and mental health composite score)	
Increased benefit in the higher Hb group for :	Lower transfusion requirements [13-15 vs >9-11.5]	
	QoL: • General health [13-15 v 10.5-12] • Vitality [13-15 vs >9-12]	

*Composite events included: time to a first CV event, death from any cause or CV event and time to death, MI, hospitalisation for CHF and stroke ‡borderline significant

Table 61: Increased risk/benefit for high/low Hb in DIALYSIS patients. Comparison: >12 g/dL versus lower Hb [The aspirational Hb levels are noted within the square brackets]

	High Hb target	Low Hb target
Increased risk in the higher Hb group for:	Access thrombosis [13-16 vs 9-12]	
No difference	• All cause mortality • CV mortality • MI • Cardiac event	

	• Hypertension • Change in LVMI • QoL (all domains with the exception of the vitality domain)	
Increased benefit in the higher Hb group for :	Lower transfusion requirements [13-15 vs 9-11.5]	
	QoL: • vitality [13-15 vs 9-11.5]	

Table 62: Increased risk/benefit for high/low Hb in NON-DIALYSIS patients: Comparison: 10 to 12 g/dL versus >9 g/dL. Comparison: >12 g/dL versus lower Hb (aspirational Hb levels are noted in parenthesis)

	High Hb target	**Low Hb target**
Increased risk in the higher Hb group for:	Hypertension	
No difference	• All cause-mortality • Progression of CKD [creatinine clearance; initiation of dialysis] • Worst LVM-change from baseline	

Comparison: >12 g/dL versus lower Hb

1. All-cause mortality

a. *Non-dialysis*

There is very low quality evidence [95,128,192,279,307,322] to show no significant difference in the risk of mortality in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups. (Figure 114, Appendix CC).

b. *Dialysis*

There is very low quality evidence[41,118,128] to show no significant difference in the risk of mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups in the dialysis population. (Figure 115, Appendix CC).

2. CV mortality

a. *Non-dialysis*

There is very low quality evidence[96,128] to show no significant difference in the risk of cardiovascular mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL). (Figure 116, Appendix CC).

b. *Dialysis*

There is very low quality evidence[41,128,272] to show no significant difference in the risk of cardiovascular mortality in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) dialysis patients. (Figure 117, Appendix CC).

3. Progression of CKD

Non dialysis

i. Mean decrease in GFR

There is moderate quality evidence[96,128,192,304,307] to show no significant difference in the progression of CKD, as determined by the mean decrease in GFR, in the higher Hb level (12 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) group. (Figure 118, Appendix CC).

ii. Creatinine clearance

There is very low quality evidence[192] to show no significant difference in the progression of CKD, as determined by the creatinine clearance, in the higher Hb level (12 to 14 g/dL) group compared with the lower Hb level (9 to 10.5 g/dL) group. (Figure 119, Appendix CC).

iii. Initiation of dialysis

There is very low quality evidence[96,192,301,304] to show a borderline increased risk of initiation of dialysis in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Figure 120, Appendix CC).

iv. Worsening renal function

There is very low quality evidence [307] to show no difference in worsening renal function in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (11 to 12 g/dL) group. (Figure 121, Appendix CC).

4. Access thrombosis [*Dialysis*]

There is very low quality evidence[41,118,128,272] to show a significant increased risk of access thrombosis in the higher Hb level (13 to 16 g/dL) group compared with the lower Hb level (9 to 12 g/dL) groups. (Figure 122, Appendix CC).

5. Transfusion

a. *Non-dialysis*

There is moderate quality evidence[96,279] to show a significantly lower number of patients transfused in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL) (Figure 123, Appendix CC).

(Reason for transfusions not reported).

b. *Dialysis*

There is moderate quality evidence[41,117] to show a significantly lower number of patients transfused in the higher Hb level (13 to 15g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group (Figure 124, Appendix CC). (Reason for transfusions not reported.)

6. Stroke

a. *Non-dialysis*

There is low quality evidence[96,279,322] to show an increased risk of stroke in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL) group. (Figure 125, Appendix CC).

b. *Dialysis*

There were no studies reporting stroke outcome in a dialysis population.

7. MI

a. *Non-dialysis*

There is very low quality evidence[96,279,307,322] to show no significant difference in myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Figure 126, Appendix CC).

b. *Dialysis*

There is very low quality evidence to show no significant difference in:

- myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group (Figure 127, Appendix CC) [41,272].
- fatal myocardial infarction in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11 g/dL) group (Figure 128, Appendix CC) [41].
- cardiac events in the higher Hb level (13 to 14 g/dL) group compared with the lower Hb level (9.5 to 10.5 g/dL) group (Figure 129, Appendix CC) [118].

8. Hypertension

a. *Non-dialysis*

There is low quality evidence[96,192,279,301,307] to show an increased risk of hypertension in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 12 g/dL) group. (Figure 130, Appendix CC)

b. *Dialysis*

There is very low quality evidence[272] to show no significant difference for the risk of hypertension in the higher Hb level(13.5 to 14.5 g/dL) group compared with the lower Hb level (9.5 to 11.5 g/dL) group. (Figure 131, Appendix CC).

9. Change in LVMI

a. *Non-dialysis*

There is very low quality evidence[96,192,301,304] which shows no significant difference in the change in LVMI in the higher Hb level (12 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group. (Figure 132, Appendix CC).

There is low quality evidence[98] to show:

- no significant difference in change in LVMI (at 1 and 3 years follow-up) in patients in the higher Hb level (13-15 g/dL) group compared with the lower Hb level (10.5-11.5 g/dL) group. (Figure 132, Appendix CC).
- a significantly greater change in LVMI at 2 years in the lower Hb level (10.5-11.5 g/dL) group compared with the higher Hb level (13-15 g/dL) group. (Figure 133, Appendix CC).

b. *Dialysis*

There is low quality evidence[272] to show no significant difference in the change in LVMI in the higher Hb level (13.5 to 14.5 g/dL) group compared with the lower Hb level (9.5 to 11.5 g/dL) group. (Figure 134, Appendix CC).

10. Quality of Life (SF-36)

A summary of the statistical significance for each of the domains for each study is reported in Table 63.

Two studies[301,304] did not report numerical values for all of the domains and one study[96] reported that there was no statistically significant difference in the QoL scores at year 3 and year 4; the numerical values were not reported.

Table 63: Quality of Life: Change in SF-36 scores from baseline [all domains]

Study	Physical function	Physical role	Pain	General health	Vitality	Social function	Emotional role	Mental health	Physical health composite	Mental health composite
NON-DIALYSIS										
ACORD [Ritz 2007]	-	-	-	NS	NS §	-	-	-	-	-
CREATE‡- [Drueke 2006] (year 1)	↑	↑	NS	↑	↑	↑	NS	↑	-	-
CREATE‡ (year 2)	NS	NS	NS	↑	↑	NS	NS	NS	-	-
CREATE ‡(year 3)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
CREATE ‡(year 4)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
CHOIR [Singh 2006]	NS	NS	NS	NS	NS	NS	↓	NS	-	-
TREAT [Pfeffer 2009] (25 weeks)	NS	-	-	-	NS	-	-	-	-	-
Roger 2004 (2 years)	-	-	-	-	-	-	-	-	NS	NS
Rossert 2006 †(4 months)	↑	↑	NS	NS	↑	NS	NS	NS	-	-
Rossert 2006 (9 months)	NS	NS	NS	NS	NS	NS	NS	NS	-	-
DIALYSIS										
Besarab * (1 year)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Besarab* (2.5 years)	↓	NS	NS	NS	NS	NS	NS	NS	↓	NS
Parfrey 2005¶ (0.9 years)	-	-	-	-	NS	-	-	-	-	-

§ACORD: Study did not report numerical values for the vitality domain but stated that the difference was not significant. ‡CREATE[302]: Additional data received upon request; numerical values not reported for years 3 and 4.

†Rossert: Data extracted from graph for QoL reported at end of stabilisation period – 4months; Only raw scores reported not adjusted for change from baseline. Additional data[155] received upon request - only raw scores reported not adjusted for change from baseline.

*Besarab[20]: Additional data received upon request. ¶Parfrey 2005- Study stated in the methods section that only SF-36 for vitality would be assessed.

↑=statistically significant in favour of the higher Hb group; ↓=statistically significant in favour of the lower Hb group NS = not statistically significant; - =domain not reported

a. *Non-dialysis*

There is very low quality evidence[96,96,279,301,307,307,322,322] (Figure 135, Appendix CC) to show:

- a significant improvement in the quality of life scores in the higher Hb level (13 to 15 g/dL) group compared to the lower Hb level (>9 to 12 g/dL) group in the following domain:
  - vitality
  - general health.
- no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group compared to the lower Hb level (>9 to 12 g/dL) group in the following domain:
  - physical function.

There is very low quality evidence[96,307,322] (Figure 135, Appendix CC) to show:

- no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group versus the lower Hb level (10.5 to 12 g/dL) group in the following domains:
  - physical role
  - pain
  - emotional role
  - social function
  - mental health.

There is very low quality evidence[304] to show:

- no difference in the quality of life scores in the higher Hb level (12 to 13 g/dL) group versus the lower Hb level (9 to 10 g/dL) group in the following domain:
  - physical health composite score.
- no significant difference in the quality of life scores in the higher Hb level (12 to 13 g/dL) group versus the lower Hb level (9 to 10 g/dL) group in the following domain:
  - mental health composite score.

b. *Dialysis*

There is moderate quality evidence[41] (Figure 136, Appendix CC) to show no significant difference in the quality of life scores in the higher Hb level (13 to 15 g/dL) group versus the lower Hb level (9 to 11 g/dL) group in the following domains:

- physical function
- physical role
- pain
- general health
- social function
- emotional role

- mental health
- physical health composite score
- mental health composite score.

There is moderate quality evidence[41,272] (Figure 136, Appendix CC) to show a significant increase in the quality of life scores favouring the high Hb level (13 to 15 g/dL) group compared with the lower Hb level (9 to 11.5 g/dL) group in the following domain:

- vitality

11. Composite events

Non-dialysis

There is moderate quality evidence[96,279,322] to show a borderline increased risk of composite events* in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (>9 to 11.5 g/dL) group. (Figure 137, Appendix CC).

* composite events were as follows:

- CREATE: time to a first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischaemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis),or cardiac arrhythmia resulting in hospitalisation for 24 hours or more.
- CHOIR: time to the composite outcome: of death, MI, hospitalisation for CHF (excluding RRT) or stroke.
- TREAT: time to composite outcome: death from any cause or a cardiovascular event (non fatal MI, CHF, stroke or hospitalisation of myocardial ischaemia).

12. CV event free survival

Non-dialysis

There is very low quality evidence[98] to show:

- no significant difference in CV event free survival (at 1, 2 and 3 years follow-up) in patients with concentric LVH at baseline in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (10.5 to 11.5g/dL) group. (Fure 137, Appendix CC).
- no significant difference in CV event free survival (at 1 year and 2 years) in patients with eccentric LVH at baseline in the higher Hb level (13 to 15 g/dL) group compared with the lower Hb level (10.5 to 11.5g/dL) group. (Firue 138, Appendix CC).
- a borderline significant higher CV event free survival (at 3 years) in patients with eccentric LVH at baseline in the lower Hb level (10.5 to 11.5g/dL) group compared with the higher Hb level (13 to 15 g/dL) group. (Figure 139, Appendix CC).

Comparison: 10 to 12 g/dL versus >9 g/dL

Non-dialysis

1. All-cause mortality

There is very low quality evidence[208] to show no significant difference in the risk of mortality in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Figure 140, Appendix CC).

2. Creatinine clearance

There is low quality evidence[208] to show no significant difference in the progression of CKD, as determined by creatinine clearance, in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Figure 141, Appendix CC).

3. Initiation of dialysis

There is very low quality evidence[208] to show no significant difference in the risk of initiation of dialysis, in the high Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Figure 142, Appendix CC).

4. Hypertension

There is low quality evidence[208] to show an increased risk of hypertension in the higher Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Figure 143, Appendix CC).

5. Worst LVM- Change from baseline

There is low quality evidence[208] to show no significant difference in the worst LVM (change from baseline) in the higher Hb level (10 to 12 g/dL) group compared with the lower Hb level group (Figure 144, Appendix CC).

6.9.4 Health economic literature review [2011]

One cost-effectiveness model comparing the treating to different Hb targets was included in the 2006 guideline and one in the 2011 update search; these were however both excluded as they were only partially applicable to the UK NHS setting and were judged to be of limited use to decision making for the guideline due to the approaches taken to the clinical data[359,360].

6.9.5 Cost of reaching targets in RCTs [2011]

The estimated cost of erythropoiesis-stimulating agent (ESA) in the different arms of the RCTs identified in the systematic review above are summarised in Figure 9 and Figure 10 below.

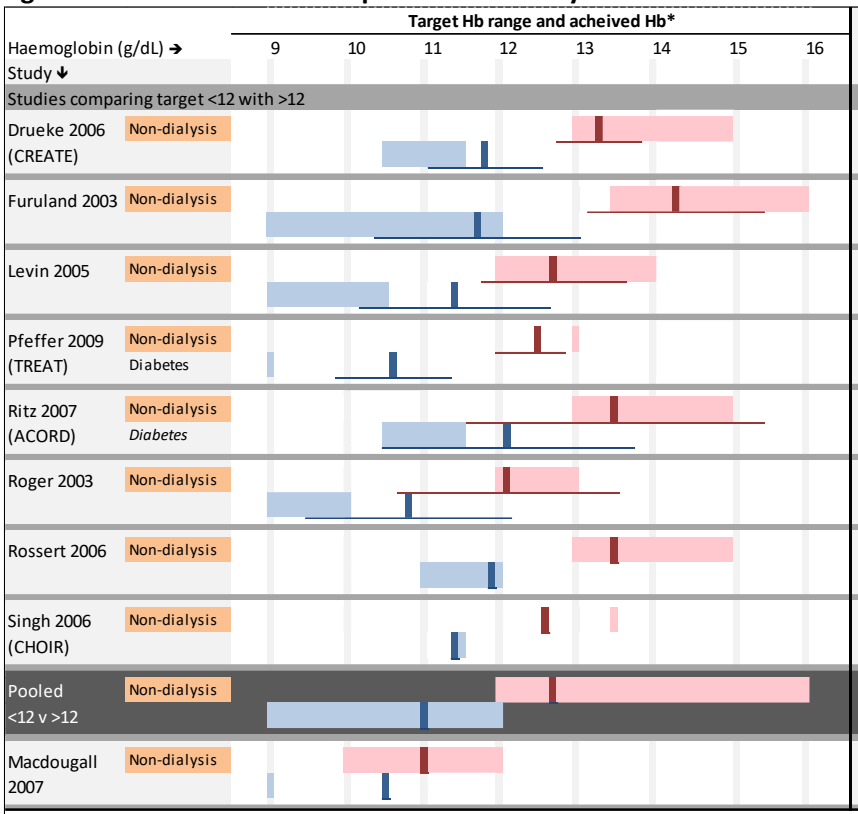
The average drug dose reported for each arm of the study was obtained. Different studies reported different measures of dose; the best available measure was used with mean preferred over median, estimates over the whole study preferred over estimates at the end of the study and units/kg/week from the study (assuming 65kg in calculations) preferred over units/week from the study.

All doses were converted to epoetin for comparison. Epoetin alfa and epoetin beta doses were assumed to be equivalent; darbepoetin dose was converted using a darbepoetin:epoetin ratio of 1:200. This is the adult conversion ratio currently stated in the UK summary of product characteristics for calculating initial dose[101]. It is noted that some studies have suggested the ratio should be higher[49] – this would increase the equivalent dose estimates for the darbepoetin study.

The cost of epoetin alfa is based on the British National Formulary list price of £5.09 per 1000 units[53]; it is noted that substantial discounts are however often available for ESAs in practice. Where data is pooled a weighted average is used based on trial patient numbers (so larger studies contribute more to the pooled estimate than smaller studies).

It was noted that in some of the dialysis studies iv or sc dosing could be used while in others only sc could be used; when iv dosing with short acting ESAs (epo alfa and epo beta) is used the ESA dose required is generally higher than when sc dosing is used.

Figure 9: Dose and cost comparison: non-dialysis studies



Study		n	FU yrs	Drug	Dose U/wk	Measure	Eqiv. dose epo	Estimated cost/year	Difference High - Low
Studies comparing target <12 with >12									
Drueke 2006 (CREATE)	Non-dialysis	301	3.0	Epo beta (sc)	4554	Estimate based on mean dose in those receiving drug at various timepoints and % that received drug over study	4554	£1,205	£628
		302		Epo beta (sc)	2182		2182	£577	
Furuland 2003	Non-dialysis	36	0.9	Epo alfa (sc)	6955	Mean at end of study (U/kg/wk, 65kg)	6955	£1,841	£1,170
		36		Epo alfa (sc)	2535	Mean at end of study (U/kg/wk, 65kg)	2535	£671	
Levin 2005	Non-dialysis	78	2.0	Epo alfa (sc)	3106	Mean at end of study	3106	£822	£619
		74		Epo alfa (sc)	768	Mean at end of study	768	£203	
Pfeffer 2009 (TREAT)	Non-dialysis	2012	2.4	Darbo alfa	56	Mean over study	11250	£2,978	£2,911
	Diabetes	2026		Darbo alfa	1.25	Mean over study	250	£66	
Ritz 2007 (ACORD)	Non-dialysis	88	1.3	Epo beta (sc)	2997	Median over study (U/kg/wk, 65kg)	2997	£793	n/a
	Diabetes	82		Epo beta (sc)	NR	NR	NR	n/a	
Roger 2003	Non-dialysis	75	2.0	Epo beta (sc)	NR	NR	NR	n/a	n/a
		80		Epo beta (sc)	NR	NR	NR	n/a	
Rossert 2006	Non-dialysis	195	1.0	Epo alfa (NR)	4352	Estimate based on median in those receiving	4352	£1,152	£911
		195		Epo alfa (NR)	910	drug and % that received drug	910	£241	
Singh 2006 (CHOIR)	Non-dialysis	715	1.3	Epo alfa (NR)	11125	Mean over study (U/kg/wk, 65kg)	11125	£2,945	£1,283
		717		Epo alfa (NR)	6276	Mean over study (U/kg/wk, 65kg)	6276	£1,661	
Pooled <12 v >12	Non-dialysis						9979	£2,641	£2,168
							1788	£473	
Macdougall 2007	Non-dialysis	65	2.0	Epo alfa (sc)	2047	Mean at end of study	2047	£542	£337
		132		Epo alfa (sc)	773	Mean at end of study	773	£205	

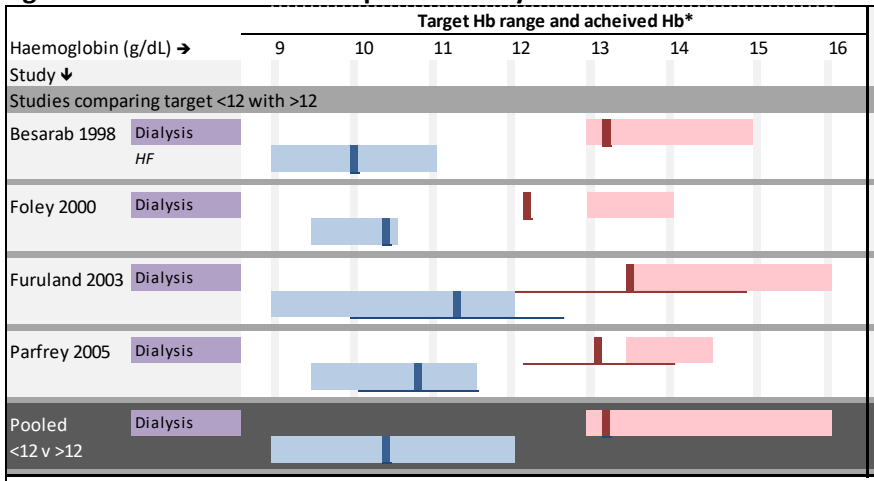
*Key:

Higher Hb	Lower Hb
Target	Target
Acheived	Acheived

underscore represents standard deviation (or interquartile range) if available

Equiv. dose epo: epoetin alfa and epoetin beta assumed equivalent; darbopoetin dose converted using a darbepoetin:epoetin ratio of 1:200.
Estimated cost/year: calculated using the British National Formulary list price of £5.09 per 1000 units for epoetin alfa[53].
Pooled: weighted average with weighting based on trial patient numbers
Sources: Dreuke[302,96], Furuland[128], Levin[192], Pfeffer[279,280], Ritz[301], Roger[304], Rossert[307], Singh[322], Macdougall[208]

Figure 10: Dose and cost comparison: dialysis studies



Study ↓		n	FU yrs	Drug	Dose U/wk	Measure	Eqiv. dose epo	Estimated cost/year	Difference High - Low
Studies comparing target <12 with >12									
Besarab 1998	Dialysis	618	1.2	Epo alfa (iv/sc)	28990	Mean over study (U/kg/wk, 65kg)	28990	£7,673	£5,006
	HF	615		Epo alfa (iv/sc)	10075	Mean over study (U/kg/wk, 65kg)	10075	£2,667	
Foley 2000	Dialysis	73	0.9	Epo alfa (sc)	18711	Mean over study (U/kg/wk, 65kg)	18711	£4,952	£2,724
		73		Epo alfa (sc)	8417.5	Mean over study (U/kg/wk, 65kg)	8417.5	£2,228	
Furuland 2003	Dialysis	180	1.2	Epo alfa (sc)	14775	Mean at end of study (U/kg/wk, 65kg)	14775	£3,911	£1,706
		159		Epo alfa (sc)	8329	Mean at end of study (U/kg/wk, 65kg)	8329	£2,205	
Parfrey 2005	Dialysis	296	1.8	Epo alfa (iv/sc)	9880	Mean over study (U/kg/wk, 65kg)	9880	£2,615	£1,273
		300		Epo alfa (iv/sc)	5070	Mean over study (U/kg/wk, 65kg)	5070	£1,342	
Pooled	Dialysis						21307	£5,640	£3,411
<12 v >12							8418	£2,228	

*Key: Higher Hb: Target, Acheived; Lower Hb: Target, Acheived; underscore represents standard deviation (or interquartile range) if available

Equiv. dose epo: epoetin alfa and epoetin beta assumed equivalent; darbopoetin dose converted using a darbepoetin:epoetin ratio of 1:200.
Estimated cost/year: calculated using the British National Formulary list price of £5.09 per 1000 units for epoetin alfa[53].
Pooled: weighted average with weighting based on trial patient numbers
HF = heart failure
Sources: Besarab[41], Foley[118], Furuland[128], Parfrey[272]

6.9.6 EQ5D utility estimates [2011]

For economic evaluation, a specific measure of quality of life known as utility is required to calculate QALYs. Utility is measured on a scale of zero to one where zero is dead and one is full health. The NICE reference case prefers utility to be assessed by the EQ5D instrument. EQ5D data was not reported in the study publications for the RCTs comparing different targets but SF36 data was commonly reported. The eight domain scores from SF36 can be mapped to a single EQ5D utility score using a published algorithm[22].

Sufficient data was available to map SF36 data from three non-dialysis and one dialysis study. Full details of mapping methods are included in Appendix W.

Table 64: EQ5D data: model inputs

	Study n overall	Mapped EQ5D				
		Target <12	*SE*	Difference	*SE*	*CI*
NON-DIALYSIS						
Drueke 2006 (CREATE)	603	0.82	*0.008*	0.033	*0.007*	*0.018, 0.047*
Rossert 2006	390	0.81	*0.012*	0.018	*0.018*	*-0.019, 0.052*
Singh 2006 (CHOIR)	1432	0.71	*0.008*	-0.006	*0.013*	*-0.025, 0.013*
Pooled‡ - Dreuke, Rossert, Singh		**0.75**	***0.005***	**0.008**	***0.007***	***-0.006, 0.021***
DIALYSIS						
Besarab 1998	1233	0.63	*0.01*	-0.003	*0.01*	*-0.029, 0.024*

‡ Pooled estimates are based on a weighted average of study averages; weighting based on number of patients in each study overall; CI = confidence interval; SE = standard error

6.9.7 Health economic modelling [2011]

In the 2006 guideline a cost-effectiveness model comparing different Hb treatment targets was developed. However, the approach taken (using cohort data) was judged by the GDG to no longer be appropriate in light of new clinical data available in the 2011 update. The 2006 analysis was therefore removed from the guideline and a new analysis undertaken as part of the 2011update.

A new cost-effectiveness analysis based on the RCT data identified in the clinical review was developed. This compared treating to a target Hb of <12g/dL and to a target of >12 g/dL in a non-dialysis population.

Full details of methods, model inputs, results and sensitivity analyses, and a discussion of limitations of the analysis, can be found in Appendix W.

Population

The non-dialysis and haemodialysis populations were considered separately by the GDG. The cost-effectiveness analysis was restricted to non-dialysis patients as there was limited SF36 quality of life data for haemodialysis patients to inform the estimate of utility for the model required to calculate QALYs.

Comparators

It was decided that the most useful and feasible option based on the available RCT data would be to compare a higher Hb target (>12 g/dL) versus a lower Hb target (<12 g/dL) based on pooled data for studies that make this comparison. Data did not allow more refined comparisons.

Note that the studies used to inform the model all compare slightly different ranges. The lower targets were in the range 9-12 g/dL and the higher targets were in the range 12-16 g/dL. Studies also varied in their baseline Hb levels and achieved Hb levels. This information is all summarised in section 6.9 of the full guideline.

It was felt that the available RCT data was insufficient to allow a comparison to be made within the lower end of the Hb range (11-12 versus 9-11 g/dL, or similar). While one RCT reports mortality data for a comparison within this range (MacDougall; n=197; RR 0.93, 10-12 vs 9), no RCTs reported EQ5D or SF36 data within this range[208].

Model overview

Costs and quality-adjusted life-years (QALYs) were considered from a NHS and personal social services perspective. In the base case analysis a three year treatment period was considered with the impact of this extrapolated to a lifetime perspective.

The model incorporated differences between the Hb targets in terms of mortality, quality of life and ESA dose based on the RCTs identified in the clinical review of the literature.

Results

Results found that treating to a higher target of >12 was not cost effective when compared to treating to a target <12. The lower target 'dominated' the higher target with less costs and better health outcomes (higher QALYs). This conclusion was robust to various sensitivity analyses.

6.9.8 From evidence to recommendations

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.

The GDG highlighted that two studies within the meta-analysis[338] included children but that no outcome data were specifically reported from this population. The GDG noted that despite a lack of direct evidence relating to children, they could in general be expected to benefit from a similar Hb level to adults.

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.

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 and 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[220]. 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[360].

The consensus among the GDG was that a range of 11.0–12.0 g/dl was consistent with both the clinical and health economic evidence.

6.9.9 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.9.9.1 Relative values of different outcomes

The GDG gave the most weight to the hard clinical outcomes of, mortality, cardiovascular events (stroke, MI) and transfusion requirements. They also acknowledged the importance of quality of life as a key goal of anaemia treatment. There were, however, limitations of the evidence on quality of life outcomes (discussed under 'quality of evidence' section).

Intermediate cardiovascular outcomes (hypertension and LV function) were given less weight but considered as important indicators of increased cardiovascular risk and future adverse outcomes.

Progression of CKD was given less weight due to difficulties in measuring and interpreting this outcome. Mean decrease in GFR, change in creatinine clearance and initiation of dialysis were all considered as indicators of progression and were considered to suggest adverse outcome.

The GDG also considered the impact of higher Hb levels on dialysis access thrombosis.

6.9.9.2 Trade off between clinical benefits and harms

The evidence for nondialysis and dialysis patients was considered separately as the underlying risk profile is different in these groups.

The GDG again noted that the interpretation of the evidence is complicated by the relationship between the target (aspirational) Hb levels in the different treatment groups in the trials and the achieved Hb levels. There was considerable variation in the doses of ESA used in the different trials and that no data were available that related the outcomes of interest to the dose of ESA used rather than the level of Hb achieved.

The GDG noted that a comparison of the outcomes above and below a Hb level of 12g/dL was the only analysis that the data allowed as this reflected the levels achieved in most studies, but they would have liked to have been able to compare outcomes above and below different thresholds.

The GDG considered the evidence in nondialysis patients which showed an increased risk for stroke (in patients with diabetes), hypertension and there was a borderline significant trend indicating increased risk for initiation of dialysis aspiring to correct anaemia to higher Hb levels (>12 g/dL).

For all-cause mortality there was a trend toward the higher target Hb group being at increased risk however this data was derived from studies powered for composite outcomes (not all cause mortality) and several of the trials were terminated early. The GDG were mindful that although there was no significant difference in all cause mortality being reported this was not considered robust enough evidence from which they could defer that there was no difference in mortality.

The GDG also considered the evidence for dialysis patients which showed an increased risk of access thrombosis with higher Hb levels.

The GDG noted that in both nondialysis and dialysis patients there was a reduction in transfusion requirements and a statistically but not clinically significant improvement in quality of life outcomes in the groups with high aspirational Hb levels (>12 g/dL) to correct anaemia.

As part of an economic model undertaken for the guideline based on the clinical studies identified in the clinical review, treating people with nondialysis CKD and anaemia to a higher Hb target (>12 g/dL) was found to result in less quality-adjusted life-years (QALYs) than treating to a lower target. The model included quality of life and mortality. While cardiovascular events were excluded, this would

only further lower the QALYs with the higher Hb target as these outcomes generally favoured the lower target.

The GDG concluded that the evidence of increased risk of adverse events outweighed beneficial effects of aspiring to a high Hb levels.

6.9.9.3 Economic considerations

The GDG considered the doses, and associated costs, of achieving the higher Hb targets in the RCTs included in the clinical review for nondialysis and dialysis populations. As might be expected, aiming for a higher target resulted in higher ESA doses being used which would result in higher costs.

It was noted that ESA doses varied between studies. US studies (such as CHOIR[322]) tended to have used considerably higher doses than European studies (such as CREATE[96]).

An economic model was built to assess the costs and QALYs of aiming for a higher Hb target (>12g/dL) with a lower target (<12g/dL) in nondialysis patients. This found that aiming for a higher target was associated with less QALYs (worse health outcome) and higher costs. This therefore suggested that a lower target was both clinically and economically favourable. This conclusion was robust to a range of sensitivity analyses including scenarios favouring the higher target.

Whilst it is difficult to extrapolate from a nondialysis population to a dialysis population, the available dialysis evidence suggested no difference in quality of life, a similar difference in mortality to nondialysis patients and larger difference in ESA dose than in nondialysis patients. It was therefore considered unlikely that results would vary in dialysis patients.

6.9.9.4 Quality of evidence

The GDG noted that the quality of the evidence ranged from moderate (composite events) to very low (all-cause mortality).

The GDG recognised that the evidence for stroke was largely weighted by the TREAT[279] study in nondialysis diabetic patients and they noted that whilst the reasons why stroke may have occurred in this population were unclear the overall evidence still shows an increased risk of stroke in the high Hb group. They also debated whether the diabetic population was fundamentally different to the non-diabetic population, or whether their higher baseline risk of cardiovascular events allowed an increased risk of adverse outcome to be observed.

The GDG noted that there were limitations in the evidence on quality of life data on the SF-36 scale. Reporting was variable and data was often not reported for all domains, the quality rating was very low in the nondialysis population, and the observed improvements in quality of life scores were small. They also discussed other limitations of the evidence, for example lack of blinding in trials, which although was a source of bias may not have affected the results as the trials still showed harms and effects of adverse outcomes.

There was no new evidence identified in young people and children and it was agreed the ranges for young people and children would be decided based on the discussions for the ranges agreed for the adult population.

6.9.9.5 Other considerations

Trials should be interpreted with care as:

- Trials were selective and baseline Hb quite high –trials did not include patients with very low Hb
    - In some studies many patients in the low Hb arm did not require treatment as they were already within the target.

- While most trials have been grouped into comparing targets of Hb >12g/dL and Hb <12 g/dL, studies were variable in terms of baseline Hb, the exact targets they compare and the Hb level achieved in each arm.
    - High (>12 g/dL) targets were all in the range of 12-16 g/dL and low (<12 g/dL) targets were in the range of 9-12 g/dL. However, high target arms systematically underachieved and low targets overachieved.

The GDG recognised that a 'one-size fits all' recommendation for an aspirational range was not practical and that recommendations should be individualised. The GDG's reasoning for this approach was based on:

- the recognition that Hb levels are not just a marker of anaemia
- some of the adverse effects observed may not necessarily be from a high Hb level in itself but may be due to using high doses of ESA to achieve the level
- acknowledgment that the evidence does not answer whether there are any benefits of a higher Hb in a young highly active patient.

The GDG were not aware of any ethnicity or diversity issues that needed to be taken into account as a result of the evidence reviewed.

In making recommendations the GDG considered:

- what the usual aspirational Hb levels should be for adults and children
- that lower levels of Hb are acceptable in patients who cannot reach the target despite treatment
- that in some situations higher levels of Hb may be acceptable and beneficial to individual patients.

Recommendation 32

The GDG debated the multi factorial elements underpinning this recommendation and considered:

- anecdotal evidence from patient representatives of the importance of the quality of life issue, especially in day-to-day living and functioning.
- that Hb is a biomarker and there are dangers in considering Hb in isolation – ESA doses required to achieve given levels of Hb are an important consideration.
- that there may be people with CKD who are at low vascular risk and low stroke risk who would derive a quality of life benefit from higher Hb levels. In these people higher Hb levels achieved with relatively low doses of ESA may be appropriate.
- that conversely people with additional co-morbidities may display different clinical indicators and signals. For example, the TREAT study was in a population of people with diabetes and CKD, a population with microvascular disease and increased risk of stroke. There is a known microvascular disease aspect to diabetes and there are pathophysiological reasons why a diabetic may be more predisposed to stroke.
- that there are elements/factors awaiting precise definition that clearly place certain groups of people with ACKD at increased risk from higher Hb levels. In these groups the evidence signals that escalating doses of ESA are associated with adverse outcome and the GDG agreed that caution should be displayed.

Recommendation 33

The GDG noted that the evidence did not support correction of anaemia to normal levels of Hb in people with CKD. The unifying feature of the studies reviewed was that viewing Hb level in isolation whilst attempting to achieve correction of anaemia to normal healthy population Hb levels was inappropriate. The evidence clearly signalled caution in trying to push people to achieve higher levels of Hb.

The consensus of the GDG was that the evidence supported reducing the aspirational Hb treatment range to 10-12 g/dL. The Hb range was kept at 2 g/dL as patients' Hb levels naturally vary and are not at a constant level therefore it is impractical to achieve a narrower range. The action thresholds were adjusted accordingly.

Recommendation 34

A separate recommendation was drafted regarding adjustment of Hb in relation to ESA doses in both patients who fail to achieve aspirational Hb levels despite high ESA doses and those unintentionally exceeding aspirational Hb levels with low doses of ESAs.

The GDG debated what would constitute 'high doses of ESA'. No upper dose limit exists in the BNF and the upper dose limits quoted in the Summary of Product Characteristics (SPC) may be higher than the doses that were associated with worse outcomes in the clinical trials and is above that thought to be clinically appropriate.

It was suggested that the doses (the median (IQR) or mean ± 2SD) in the predominantly European trials (e.g. CREATE), could used as a guide. However it was felt that the trial populations may be unrepresentative of the whole population of people with anaemia of CKD. The GDG decided to refer to UK clinical practice as reflected in the UK Renal Registry data, recognising that these encompass patients with predominantly dialysis-dependent CKD.

The following recommendation was deleted because it was decided to be more cautious given the findings of the review and the guidance from the Medicines and Health Regulatory Agency with regard to the increased risk of mortality and cardiovascular morbidity associated with higher levels of haemoglobin.

Consider accepting Hb levels above the agreed aspirational range when:

- these develop with iron therapy alone or
- these develop with low doses of ESAs or
- it is thought that the person might benefit (for example, if they have a physically demanding job), or
- the absolute risk of cerebrovascular disease is thought to be low.

6.9.9.6 Future research recommendation

Future research should look to stratify patients randomised to different target ranges of Hb by responsiveness to ESA in terms of maintenance EPO dose/kg body weight/maintenance Hb level achieved before analysing outcomes.

6.10 Optimum haemoglobin levels in children with anaemia of CKD [2006]

6.10.1 Methodological introduction

The two RCTs reported in the meta-analysis[338] conducted in children[52,230] – one of cross-over design[230] – were used to address the effects of lower vs higher haemoglobin and were individually appraised. An additional cross-over RCT[231] that was conducted in the same paediatric population was also appraised.

Issues for consideration were as follows:

- The two cross-over RCTs[230,231] were downgraded to Level 2+ because of methodological limitations.

- One study[52] had set out to investigate dosing requirements.
- Study duration to assess cardiovascular benefits of epoetin administration[231] may not have been sufficiently long at 48 weeks.

Table 65: Summary characteristics of appraised studies

Study	N	Target Hb	Study type	Study duration
[52]	44	Between mean and 2 standard deviations below mean for age	RCT of low dose vs high dose epoetin	12 weeks
[231]	7	10.5–12.0 g/dl	Cross-over RCT of epoetin vs placebo	24 weeks in each limb, 48 weeks total
[230]	7	10.5–12.0 g/dl	Cross-over RCT of epoetin vs placebo	24 weeks in each limb, 48 weeks total

6.10.2 Evidence statements

Table 66: Evidence statements for optimum Hb levels in children

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
[52]	Systolic and diastolic BP No difference	Children on haemodialysis, peritoneal dialysis and predialysis (n=44)	12.9 ± 0.7; 11.9 ± 1.6; 12.7 ± 2.0 g/dl	8.4 ± 1.0; 10 ± 2.04; 11.9 ± 1.8 g/dl	Level 1+
[231]	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. There was no change	Children on peritoneal dialysis (n=7)	11.5 g/dl (target 10.5–12.0 g/dl)	6.9 g/dl	Level 2+

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
	in shortening fraction, interventricular septum and left ventricular posterior wall thickness. No change was found in systolic, diastolic or mean BP.				
[230]	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.	Children on peritoneal dialysis (n=7)	Median 11.2 g/dl (range 9.5–14.2 g/dl)	Median 7.3 g/l (range 4.2–8.1 g/l)	Level 2+
[230]	Quality of life (25-part parental questionnaire, using a visual analogue scale) found an	Children on peritoneal dialysis (n=7)	11.2 g/dl (range 9.5–14.2 g/dl)	Median 7.3 g/l (range 4.2–8.1 g/l)	Level 2+

Study	Hypertension and cardiovascular parameters	Patient population (n)	Achieved high Hb	Achieved low Hb	Evidence grading
	improvement in physical and general health (p<0.02), but the global score did not find an improvement in quality of life.				

6.10.3 From evidence to recommendations

The use of exercise testing for outcomes is not meaningful in very young children, which exacerbates the problem of the small sample size in the evidence.

6.10.4 Recommendations

Recommendations pertaining to children with anaemia of chronic kidney disease are presented in relevant sections throughout the guideline.

Optimum haemoglobin levels in children with anaemia of CKD [2011]

Two RCTs[52,231] identified in a paediatric population in the original guideline were further assessed. One study was an RCT of low dose versus high dose epoetin and the other study was a cross-over RCT comparing rHuEPO versus placebo.

The characteristics of the included studies are reported in Appendix BB.

Evidence profile

The evidence profile summarises the quality of the evidence and outcome data for the 2 RCTs (Table 67 to Table 69) included in this review. Results are presented by outcomes and results for the non-dialysis and dialysis populations are presented separately.

Table 67: Non-dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	8.35(SD1.1) g/dL compared to lower Hb(8.68(SD0.9)) level for children - non-dialysis	control	Relative (95% CI)	Absolute	Quality
Proportion of patients transfused - 12.7 v 11.9											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/12 (8.3%)	0/13 (0%)	RR 3.23 (0.14 to 72.46)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding
[2] 95% CI include both the line of appreciable benefit and harm

Table 68: Dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	7.23(SD) to 9.18(SD1.1) g/dL compared to lower Hb (6.78(SD1.0) to 7.68(SD1.3))evel for children - dialysis	control	Relative (95% CI)	Absolute	Quality
Proportion of patients transfused-haemodialysis - 12.9 v 8.4											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/3 (0%)	3/6 (50%)	RR 0.25 (0.02 to 3.71)	375 fewer per 1000 (from 490 fewer to 1355 more)	⊕⊕OO LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding
[2] 95% CI includes both the line of appreciable benefit and harm

Table 69: Dialysis and non-dialysis

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	11-12 g/dL compared to lower Hb level for children - both dialysis and non-dialysis	control	Relative (95% CI)	Absolute	Quality
LVMI (g/m2) after first 24 weeks group 1 - treatment, group 2 - placebo - 11.5 V 6.9 (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4	3	-	MD 13.6 higher (31.51 lower to 58.71 higher)	⊕OOO VERY LOW
LVMI (g/m2) after second 24 weeks group 1 - placebo, group 2 - treatment - 11.5 v 6.9 (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4	3	-	MD 57.1 higher (7.64 to 106.56 higher)	⊕OOO VERY LOW

[1] Brandt 1999; 1/1 had unclear allocation concealment and no report of blinding

[2] 95% CI includes both the line of appreciable benefit and harm

One study[52] either did not report the numerical values (outcome: progression of CKD) or did not report the numerical value for each treatment group (outcome: hypertension). The results for progression of CKD and hypertension are summarised in the evidence statements below with evidence statements for the outcomes transfusion rates and change in LVMI.

1. Progression of CKD

a. Non-dialysis

One study[52] reported that the change in creatinine during the study was 'insignificant' between the dosing groups and within the nondialysis group. There were no numbers reported to determine whether this difference was significant or not.

b. Dialysis

One study[52] reported that the change in creatinine during the study was 'insignificant' between the dosing groups and within the haemodialysis and peritoneal dialysis groups. There were no numbers reported to determine whether this difference was significant or not.

2. Hypertension

a. Non-dialysis

One study[52] reported that the 33% (3/9) children had new or worsening hypertension.

b. Dialysis

One study[52] reported that the 66% (6/9) children had new or worsening hypertension in the haemodialysis group and 30% (3/10) had new or worsening hypertension in the peritoneal dialysis group. Results for the high dose and low dose groups were not reported separately.

3. Transfusion rate:

a. Non-dialysis

There is low quality evidence[52] to show no significant difference in the proportion of patients transfused in high dose Hb group compared with low dose Hb group (Figure 145, Appendix CC).

b. Dialysis

There is low quality evidence[52] to show no significant difference in the proportion of patients transfused in high dose Hb group compared with low dose Hb group (Figure 146, Appendix CC).

4. LVMI

There is very low quality evidence[231] to show :

- no significant difference in LVMI at 24 weeks between the groups that received rHuEpo versus placebo. (Figure 147, Appendix CC)

- a significant increase in LVMI at 48 weeks favouring the group that received placebo followed by rHuEPO compared with the group that received rHuEPO prior to placebo (Figure 147, Appendix CC).

6.11 Adjusting ESA therapy [2006]

6.11.1 Clinical introduction

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 (ie at what haemoglobin level), and by how much to change the ESA dose and/or frequency. ESA therapy (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 therapy, haemoglobin levels fluctuate widely and the pattern of fluctuation varies from patient to patient[181]. 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[107].

Experimental and clinical studies have defined a desirable outcome range of haemoglobin and have used the limits of the range to trigger a dose change when 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 therapy pre-emptively prior to the haemoglobin level breaching the limits of the desirable range. There are also individual variations in the response to ESAs that may be taken into account from historical data. The case mix and treatment history of any patient cohort will also influence the outcome and while tailoring of the timing and dose changes may be attempted there is inevitable unpredictability of outcome.

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

A literature search found 13 studies: an RCT[235], prospective cohort studies[17,258], retrospective cohort studies[78,215,299], cross-over studies[6,252], retrospective longitudinal studies[69,385], and cross-sectional studies[140,165,200].

One study[217] 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

One study[69] 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

Three studies found epoetin dose to be inversely correlated with iron status when measured by means of serum transferrin saturation (p=0.0001)[69], serum saturation ratio (r=−0.16, p=0.003)[165] and total iron binding capacity levels (r=0.27, p<0.01)[215]. (Level 3 and Level 2+)

In contrast, one study[215] did not find an association with serum transferrin saturation. Also, no association between epoetin dose and serum ferritin levels was found in two studies[69,215]. (Level 3 and Level 2+)

Dialysis adequacy

Haemodialysis patients

One study[69] found an inverse correlation between urea reduction ratio and administered epoetin dose (p<0.0001). (Level 3)

Cause of end stage renal failure

Haemodialysis patients

One study[69] found diabetes mellitus as the cause of end stage renal failure to be associated with lower epoetin doses (p=0.003). (Level 3)

Inflammation

Haemodialysis patients

One study[165] found a direct correlation between administered epoetin dose and malnutrition-inflammation score (ie increasing degree of severity) (r=0.13, p=0.03). This was reflected in the direct correlation between weekly epoetin dose and logarithmic inflammatory cytokines, IL-6 (r=0.31, p<0.001) and TNF-α (r=0.18, 0.001) as well as C-reactive protein (CRP) (r=0.18, p<0.001) and lactase (p<0.001) levels. Similarly, there was an inverse correlation observed between epoetin dose and nutritional markers (r=−0.19, p<0.001).

In another study[140], 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 epoetin:Hct ratio. When patients in the lowest and highest epoetin:Hct quartiles were compared, only median CRP showed statistical significance (p=0.009). (Level 3)

Contrary to the above findings, in one study[200] C-reactive protein levels did not show any association with epoetin dose. (Level 3)

Peritoneal dialysis patients

In one study[140], 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

When compared with one another in the same study[140], 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

Higher epoetin doses were administered to patients receiving ACE-inhibitor therapy when compared with those not treated with ACE-inhibitors (p<0.05) in one study[215]. In a 12-month study[17], 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 with 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[258], 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 with those receiving amlodipine (calcium-channel blocker) (p<0.0001) or control (epoetin only) (p<0.0001). (Level 2+)

In contrast to the above findings, two studies with patients receiving ACE-inhibitors[6,78] 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

Weekly epoetin dose given to maintain Hct >30% (Hb ~ 10 g/dl) at the end of a 12-week study[235] was greater in patients receiving ACE-inhibitors (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 with 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

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), phosphorus (p=0.001) and calcium x phosphorus product (p=0.009)[252]. (Level 2+)

Hospitalisation

Haemodialysis patients

In one study[385], higher epoetin doses were required in patients who were transfused during hospitalisation up to 2 months following discharge (p<0.05). (Level 3)

The same study[385] 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

One before and after study (n=72)[115] 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 parts per million (ppm) to <0.1 ppm. This was supported by findings in a subgroup 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 two 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[299], 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 with other local dialysis units. These findings were associated with a high chlorine water content relative to the desirable limit (p value 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

The appraised study[282] performed a decision analysis comparing three dosage regimens: epoetin-6 strategy, 6,000 U (107 U/kg), epoetin-9 strategy, 9,000 U (167 U/kg) and epoetin-12 strategy, 12,000 U (211 U/kg) of subcutaneous epoetin in continuous ambulatory peritoneal dialysis to maintain the target Hct level of 0.33 (equivalent to 11 g/dl)[282]. 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 6,000 U and 9,000 U after 2 months entered 12,000 U regimen.

6.11.5 Health economics evidence statements

Of the three subcutaneous epoetin strategies compared, it was most cost effective in peritoneal dialysis patients to give 6,000 units weekly for 2 months, followed by a weekly or 2-weekly epoetin 6,000 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[282]. The savings from the lower administration frequency of the 9,000 unit dosage regime were offset by the higher cumulative acquisition cost[282].

Varying the parameters over the 20-week treatment period:

- Epoetin-6 strategy is always the least costly over the $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.

Varying the parameters over a 1-year treatment period:

- Epoetin-6 was less costly than both epoetin-9 and epoetin-12 over the range of costs ($0–60).
- Epoetin-6 becomes more costly than epoetin-12 at $95.
- Epoetin-6 was 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 [2006, amended 2011]

Of all of the outcomes considered in the evidence, the GDG felt that the route of ESA administration, the patient's 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 patient's haemoglobin level
- the observed rate of change in haemoglobin level
- an individual patient's response to ESA therapy.

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.

With regards to the route of administration, two studies reported that doses of short-acting ESAs could be reduced when administered subcutaneously as opposed to intravenously[69,217]. It was noted that the decision of whether to administer ESAs s.c. or i.v. was also a matter of patient choice.

Several studies supported the view that the amount of ESA required is inversely correlated with iron status[69,165,217]. 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.

The GDG noted that there was evidence to support a correlation between the weekly dose administration of ESA and inflammatory cytokines (IL-6, TNF-alfa)[165].

The GDG noted that the evidence supported the intuitive notion that sicker patients generally require higher doses of ESAs[140]. 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.

The GDG discussed the evidence with respect to adjunctive medical treatment, that patients receiving either ACE inhibitor therapy or angiotensin-II receptor antagonists required an increased dose of ESA in comparison with those patients administered a calcium-channel blocker or to control groups[215,258]. Two further studies reported no association between ACE-inhibitor administration and resistance to ESAs[6,78]. The GDG considered one study to have methodological limitations due to the non-randomised study design[6]. 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.

The GDG discussed the implications of dialysis water purity on ESA administration, in particular the GDG noted that increased chloramine levels (formed by the combination of free chlorine and ammonia gas) were associated with a need for higher doses of ESAs in haemodialysis patients[115,299]. 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 (point 2.19), and specifically notes that 'carbon filters should be selected to achieve sufficient contact time to remove all chlorine and chloramines' (point 6.78)[254]. This issue was considered an issue for a dialysis unit rather than the individual patient but the information may be of use to unit managers. The GDG concluded that dialysis units should consider the use of carbon filters but that a risk–benefit analysis should be used to assess the benefits of reducing chloramines levels against the risk of infection of the carbon filters.

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 patient's response to Hb but that in general, 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.

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 healthcare 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.

This section was outside the scope of the 2011 rapid partial update. However, when reviewing the recommendations as a whole, the GDG felt that slight changes to recommendations 38 and 40 below were necessary. This was to increase patient safety through emphasising the requirement to optimise iron status before either initiating ESA therapy or escalating ESA doses. In fact, optimisation of iron status prior to administration of ESAs, and continued optimisation of iron status during maintenance treatment with ESAs is an essential part of anaemia management because it allows ESA dosages to be kept to a minimum. This avoids the risk of higher doses of ESA, which have been associated with adverse patient outcomes. In addition, these changes that emphasise the importance of iron status in recommendations 38 and 40 below are consistent with and complement the existing recommendations **Error! Reference source not found.** and **Error! Reference source not found.**. [2011]

6.11.7 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.12 Concurrent illness [2015]

6.12.1 Introduction

If a patient receiving treatment with an ESA for anaemia of CKD develops an acute illness, such as pneumonia or an infected foot ulcer, it is likely that their anaemia will worsen. This is because firstly, any ongoing inflammatory process (such as acute infection) causes ESAs to be less effective. Secondly, the acute illness itself might aggravate anaemia. The worsening anaemia could lead to new or more severe symptoms.

In these situations, there are several possible management options to try and maintain or improve haemoglobin (Hb) levels. One option may be to acknowledge that ESAs will be ineffective during the course of the acute illness and therefore to discontinue them until recovery, using blood transfusions intermittently if necessary. This approach would save the cost of ESA used, perhaps ineffectively. Alternatively, the ESA dose could be increased in an attempt to achieve some benefit from the drug and thereby to reduce the frequency of transfusion requirement. A further option would be to continue the patient's usual dose of ESA and offer transfusions when indicated.

Each of these options has potential merits and disadvantages. For example, discontinuation of ESA might save money if it was completely ineffective, but a decision is then required on when to restart it. The time of restart might then influence the patient's anaemia management for several weeks subsequently. Use of high-dose ESA might reduce transfusion requirement, thus reducing associated (albeit relatively rare) risks of transfusion reaction, antibody generation or virus transmission. On the other hand, very high-dose ESA might increase risk of other adverse effects or might simply waste more money if it had no effect on transfusion rate.

The GDG therefore wished to establish which of these treatment strategies is the best in terms of clinical outcomes, patient satisfaction and cost-effectiveness.

6.12.1.1 Review question: What is the optimal management of anaemia of CKD in hospitalised patients who are on ESAs and have a concurrent acute infectious illness?

For full details see review protocol in Appendix C.

Table 70: PICO characteristics of review question

Population	Anaemia of CKD patients with an acute (illness of <2 weeks) infectious disease including: • Pneumonia • Urinary tract infection • Cellulitis • Sepsis • Peritonitis • Acute endocarditis • Acute osteomyelitis • Known bacterial infections.
Intervention(s)	Stop ESA and transfuse as needed
Comparison(s)	Continue ESA therapy
Outcomes	Critical (treatment-related outcomes) • Improvement in Hb levels • Number of units transfused • Average ESA use per patient Important • Length of hospital stay • In-hospital mortality • Health-related quality of life (HRQoL)
Study design	RCT or large (n=>100) observational cohort studies

6.12.2 Clinical evidence

No relevant clinical studies were identified for this clinical review.

6.12.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

6.12.4 Evidence statements

Clinical

No relevant clinical evidence was identified.

Economic

No relevant economic evaluations were identified.

6.12.5 Recommendations and link to evidence

Relative values of different outcomes	The GDG discussed the relative values of different outcomes and agreed that the treatment-related outcomes were critical for decision making. These included improvement in Hb levels, number of units transfused and average use of ESA per patient. Other outcomes were also considered important for decision making and these include length of hospital stay, in hospital mortality and HRQoL.
Trade-off between clinical benefits and harms	There are potential harms to transfusions in patients with anaemia of CKD (particularly fluid overload and sensitisation), although, there are also benefits to treating anaemia during a period of concurrent illness when symptoms of anaemia may be impairing the recovery of the patient.
Economic considerations	It is recognised that if ESA therapy is continued even though the patient will not respond to the treatment due to infection, then this is a wasted resource.
Quality of evidence	No evidence was found evaluating the use of ESA in concurrent illness.
Other considerations	The GDG discussed specific considerations with respect to the use of ESA therapy in patients who had an acute illness. They noted that illness duration longer than two weeks was outside the scope of this work and that this time frame defined the nature of 'acute' infectious illness considered in this review. CG114 (7.4.1 Managing ESA resistance - Clinical introduction) identified that infection and inflammation are the commonest causes of ESA resistance. The pro-inflammatory cytokine release accompanying such illness is believed to mediate the ESA resistance. The GDG noted that the trials of erythropoietin and related ESAs have typically recruited stable CKD outpatients, without any acute illness, and therefore, studies excluded any patients with an acute infectious illness. Thus, it was not surprising to the GDG that there was a lack of evidence to guide practice in these circumstances. For an inpatient with anaemia of CKD and an acute infectious illness, such as a lower respiratory tract infection, there are two issues about ESA use: • Whether and when the patient's anaemia will respond to ESA administration. • ESA supply and administration in an inpatient setting The GDG were aware that there is also a caution against using IV iron during infection. They noted that the lack of response may be partly due to the lack of availability of iron for haematopoiesis.

	The GDG discussed the challenges for clinicians in being aware of any ESA therapy when patients with anaemia of CKD were admitted with an acute illness and therefore potentially limiting timely decisions about treatment. Many patients with anaemia of CKD do not have their ESA supplied by the GP; instead ESAs are supplied by the renal units. Consequently, ESA therapy may not always be recorded on GP medication records, which are often the primary source of information to reconcile medication on admission. The GDG noted that hospitals should have systems in place to ensure that CKD patients are reviewed about their ESA therapy on admission. Furthermore, they felt that prescription and administration of established ESA therapy, when appropriate, should not be delayed purely as a result of the admission. NICE already recommends that medicines review and reconciliation should occur within 24 hours of admission to hospital. If the clinician is uncertain about ESA administration in the context of co-presenting acute infectious illness, the GDG agreed that specialist advice should be sought from a nephrologist, renal pharmacist, or anaemia nurse specialist or coordinator. The clinician should liaise with the renal unit on restarting ESA or discharging the patient with anaemia of CKD to ensure appropriate arrangements are in place for their continuing care. The GDG noted that, in their opinion and experience, patients with anaemia of CKD and a concurrent illness, would most likely continue with ESA and their anaemia be reviewed and monitored, particularly if the anaemia has worsened. If the concurrent illness was causing a worsening of the anaemia, then the GDG noted that early follow-up during and after recovery would be essential. However, in the absence of evidence for this question, the GDG decided it would be inappropriate to make any consensus recommendations in this topic area. As this is an important issue in clinical practice and there is a lack of evidence to inform practice, the GDG agreed that further research would help clinical decision making and made a research recommendation (see Research recommendation).

6.12.6 Research recommendation

Research question:

What is the optimal management (in terms of clinical and cost effectiveness) of anaemia of CKD in patients who are receiving ESAs and have a significant concurrent acute infectious illness?

Why this is important

Chronic kidney disease is a risk factor for mortality in patients who develop acute illness. Acute illness in CKD patients is associated with development, or worsening, of anaemia.

The anaemia of end-stage renal disease is managed primarily with ESAs and intravenous iron. When CKD patients develop acute illness, their anaemia becomes difficult to control. Acute inflammatory response usually renders patients hyporesponsive to treatments for anaemia. In addition, intravenous iron might promote bacterial infection. Many patients may end up having a blood transfusion – in part because of the lack of established guidelines on managing anaemia in CKD patients with acute illness. Little is known about the relative safety of transfusion compared with parenteral iron therapy, with or without ESA therapy.

There is a need for long-term observational studies, as well as prospective randomised controlled trials to compare the effectiveness and safety of treating anaemia in acutely ill CKD patients with parenteral iron, erythropoiesis stimulating agents, blood transfusion or a combination of the 3 different therapies. A large epidemiological or cohort study is needed with a control group (for example, patients admitted to hospital as an emergency with an acute illness, but without anaemia). The study should be adequately powered to detect factors predictive of important end points such as

patient survival, deterioration of renal function, the need to initiate renal replacement therapy and prolonged hospital stay.

Table 71: Criteria for selecting high-priority research recommendations

Criterion	Explanation
PICO question	What is the optimal management of anaemia of CKD in hospitalised patients or outpatients who are on ESAs and have a significant[e] concurrent acute infectious illness? Population: Anaemia of CKD patients with a stable anaemia regime, and with an acute (illness of <2 weeks) infectious disease, including infections listed below (but not necessarily limited to these): • Pneumonia • Urinary tract infection • Cellulitis • Sepsis • Peritoneal dialysis peritonitis • Acute endocarditis • Acute osteomyelitis • Known bacterial infections. Interventions: • Stop ESA for defined time (suggested 2 weeks) and transfuse as required, for example for Hb <100 g/litre) Comparison: • Continue ESA at prior dose and rescue transfusion as required • Increase ESA by a prespecified percentage (for example, 25%) and rescue transfusion as required Outcomes: Critical (treatment-related outcomes) • Improvement in Hb levels • Number of units transfused • Average ESA use per patient Important • Length of hospital stay • In hospital mortality • HRQoL • NHS cost and cost-effectiveness
Importance to patients or the population	People with CKD have a higher risk of hospitalisation and mortality due to infection when compared with the general population.[237,309,310,365] Infection and inflammation are recognised as causes of hyporesponsiveness or resistance to ESAs.[7,140,145,158]. Any concurrent acute infectious illness can result in worsening anaemia in patients with CKD. Blood transfusion has associated risks, including sensitisation that may limit chances of future transplantation. It is important to avoid unnecessary blood transfusions in those suitable for transplantation (of particular relevance to the paediatric population). Guidance on optimal management of anaemia during a concurrent acute infectious illness is relevant to patients, in terms of their immediate quality of life (relief of symptoms of anaemia during acute infectious illness, functional status and ability to live independently, possible prolonged inpatient stay as a result of untreated anaemia) and their longer term quality of life (including the chances of renal transplantation).
Relevance to	The answer to this question will allow NICE to make a definitive statement on the use of

[e] A significant infectious illness would obviously need to be predefined.

Criterion	Explanation
NICE guidance	ESA and blood transfusions in the treatment of anaemia of CKD in hospitalised patients who have a concurrent acute infectious illness.
Relevance to the NHS	Both ESA and blood transfusion have associated financial costs. By identifying the optimal way to manage anaemia of CKD in the context of acute infectious illness, the cost of unnecessary or ineffective treatment will be reduced. It is possible that the length of hospital stay is prolonged in patient with suboptimally managed concurrent anaemia, and this could be reduced by identifying the optimal management.
National priorities	NHS outcomes framework 2013/14: Enhancing quality of life for people with long-term conditions.
Current evidence base	None – see above.
Equality	The intervention of blood transfusion/rescue transfusions may not be possible in studies looking at: • Jehovah's witnesses/avoidance of blood products. • Patients at risk of sensitisation.
Study design	RCT or large (n=>100) observational cohort studies
Feasibility	The trial designers could consider recruiting ESRD outpatients on a stable ESA regime, preparing them for the study in advance of any concurrent infection. There may be challenges in recruiting patients admitted to a non-renal ward, as there may be a delay in recognition that the patient has anaemia of CKD, and hence randomisation into the trial. It should, however, be feasible to achieve the target recruitment numbers as anaemia of CKD and acute infectious illness occurs frequently. Highly sensitised patients would need to be excluded.
Other comments	No comments.

6.13 Treating iron deficiency: correction [2006, 2015]

6.13.1 Clinical introduction

While there are many different preparations of oral iron available (see Table 72), 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.

This table detailing the availability of iron preparations in the UK and their content has been updated and can now be found in Section 6.15

Table 72: Iron content of different oral iron preparations[a]

Iron salt	Dose	Content of ferrous iron
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous succinate	100 mg	35 mg
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate, dried	200 mg	65 mg

*(a) Please see the updated **Error! Reference source not found.** in Section 6.15with the current list of licensed preparations*

Oral iron preparations contain varying amounts of ferrous iron, and 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.

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 and sweating.

Intestinal iron absorption declines as serum ferritin increases[177,178] and ESA administration boosts iron absorption in erythropoietin deficient haemodialysis patients[325]. Patients with CKD who have anaemia, a GFR below 40 ml/min, and are not receiving ESA therapy are likely to be erythropoietin deficient[104]. 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 i.v. iron and early use of i.v. iron employed low doses given relatively frequently and administered as an infusion. Frequent administration of i.v. iron in haemodialysis patients is made feasible through use of dialysis vascular access but in peritoneal dialysis and predialysis patients venous access is required for each dose. Administration of higher doses in CKD patients not on haemodialysis offers the potential to spare venous access, but at the possible expense of increased adverse effects.

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 [147] 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 vs intravenous iron.

Iron therapy in haemodialysis patients is an essential adjuvant to ESA therapy and adequate iron stores are required prior to treatment with ESAs to ensure effective erythropoiesis. Virtually all haemodialysis patients will require ESA therapy to achieve target haemoglobin levels. By contrast, a significant proportion of predialysis 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.

6.13.2 Methodological introduction

A comprehensive literature search identified one RCT[366] investigating the efficacy of oral vs i.v. iron in predialysis patients without concurrent ESA therapy and two before and after studies investigating the efficacy of i.v. iron over 6 months[320] or as a single dose[21] in iron-deficient predialysis patients who had not previously received ESA therapy. A further before and after study was identified investigating the efficacy of i.v. iron over 12 months[223].

One study[47] did not meet quality criteria and was therefore excluded from the evidence statements.

6.13.3 Evidence statements

Iron dextran: predialysis patients

Following administration of 1g iron dextran in 500 ml normal saline i.v. 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 with 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 blood pressure did not change after 12 weeks[21]. (Level 3)

Ferric saccharate (also known as ferric hydroxide sucrose or iron sucrose): predialysis patients

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 i.v. iron dose of 1,000 mg per patient (n=33). After 3 months of i.v. iron treatment, the mean Hct and Hb values were not significantly increased, despite raised serum ferritin levels compared with baseline ($p<0.05$). At 6 months, however (ie 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 i.v. 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 blood pressure) either before or after onset of i.v. 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[320]. (Level 3)

In a study of pre-dialysed chronic renal failure patients with haemoglobin levels less than 11g/dl who were not receiving erythropoietin (n=60)[223], monthly intravenous administration of 200mg of iron sucrose for a period of 12 months was associated with a significant increase in haemoglobin from 9.7 ± 1.1 at baseline to 11.3 ± 2.5g/dl after 12 months ($p<0.05$): a mean increase of 1.6g/dl. No worsening of renal function, no increase in blood pressure and no other side effects were noted. (Level 3)

Oral vs i.v. iron sucrose: predialysis patients

In a RCT[366] investigating i.v. 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 i.v. 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 (ie rise in Hb ≥1.0 g/dl) ($p=0.0344$) and the mean increase in Hb were higher in the i.v. group by day 42 ($p=0.0298$). Notably, the difference in ESA use in achieving primary end point in the i.v. and oral group was not found to be significant. Three patients in the i.v. 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 i.v. iron administration. Constipation, diarrhoea, nausea, vomiting and dyspepsia were associated prominently with oral iron therapy, while headache, myalgia and hypotension were exclusively associated with i.v. iron administration. (Level 1++)

6.13.4 Health economics methodological introduction

One study was found but did not meet quality criteria[80]. 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.

6.13.5 From evidence to recommendations

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 therapy. 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).

6.13.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.14 Treating iron deficiency: maintenance [2006, 2015]

6.14.1 Clinical introduction

See 6.13.1.

6.14.2 Methodological introduction

Because of the high number of retrieved studies in the literature search, these were grouped into:

- induction iron therapy for iron deficiency (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 included in the evidence statements were selected on the basis of evidence level hierarchy.

Two studies[9,156] did not meet quality criteria and were therefore excluded from the evidence statements.

Notable aspects of the evidence base were:

- Three studies were conducted in children[84,371,372].
- Study durations ranged from 12 weeks to 18 months, which has implications on the time required to measure stability of treatment outcomes.

The GDG agreed that the following outcomes were priorities:

- epoetin dose
- efficacy/Hb response
- compliance
- patient preference
- side effects
- safety.

Following the first consultation on the guideline drafts, the GDG also considered additional retrospective studies[30,64,65,112,114,370] on the incidence of adverse events with intravenous iron. These papers did not report whether patients had previously had ESA therapy or not and because of potential confounding were not added as evidence statements but are discussed below under 'from evidence to recommendations' (see section 6.14.6).

6.14.3 Evidence statements

Oral iron vs intravenous iron

Two RCTs[108,205] in adult dialysis patients with serum ferritin levels >100 µg/l compared i.v. and oral iron. One study[108] (n=52, all haemodialysis) administered 100 mg i.v. iron dextran twice a week and the other[205] (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 i.v. iron to be superior. In one study[108] haematocrit increased ($p<0.05$)

and ESA dose fell (p<0.05); in the second study[205] haemoglobin increased (p<0.05) compared with those treated with oral iron. (Level 1+)

A study in predialysis patients[337] 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 significant difference in haemoglobin level or ESA requirement was observed. (Level 1++)

In a 29-day study with follow-up after 14 days[61] patients were randomised to epoetin and intermittent i.v. 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 i.v. 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 two treatment groups. However, when patients were stratified by a baseline serum ferritin < or ≥100 µg/l, the i.v. iron group had a greater increase in Hb at follow-up compared with oral iron patients (p<0.05). Also, more patients in the i.v. iron group attained Hb >11.0 g/dl compared with the oral iron group (p=0.028) and the percentage change from baseline to follow-up for both Hb and ferritin was significantly greater for the i.v. iron group (p<0.0001). Mean treatment concordance assessed by tablet counts was lower in the oral iron group (85.5%) compared with the i.v. iron group (95.0%); no p-value was reported. GI side effects were more common in the oral iron group and taste disturbances in the i.v. iron group. No patient required discontinuation of iron treatment in either group. (Level 1+)

In a study conducted in peritoneal dialysis patients[13] 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 1 month. (Level 2+)

One study conducted in children with TSAT>20%[371] randomised them to intravenous iron dextran or oral ferrous fumarate (n=35, all haemodialysis). Doses were based on weight; ferrous fumarate varied between 4 and 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[206], p<0.05[42], p<0.001[300]. One study[206] (n=116) used iron sucrose 100 mg post-haemodialysis. Another study[42] (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[300] (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 i.v. 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[318] stratified patients' responses to 20 mg intravenous iron saccharate given 3 times a week over a 6-month period by ferritin <100 µg/l (n=17) vs ≥100 <400 µg/l (n=16). Haemoglobin levels (p<0.0001) increased and ESA levels decreased (p<0.003) in all patients compared with baseline but there was no difference between groups. Four patients reported a metallic taste in association with iron but no other adverse events were reported. (Level 2+)

A further observational study[319] 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[15,26,167,308]. In three studies conducted in haemodialysis patients the same total dose of iron was administered. One study[167] 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 with the iron–treated groups. The only difference in the iron treated groups was a lower ESA requirement compared with baseline (p<0.01) in those given sequential treatment after each dialysis. One study[308] gave a total of 600 mg iron dextran (n=43). Patients received either a single bolus dose, six divided doses of 100 mg following consecutive dialyses, or 100 mg/week for 6 weeks. No difference was observed 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 three different iron dextran regimens[26]. 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[15] gave a total dose of intravenous ferric saccharate of 600 mg in divided doses with two 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 with those given 100 mg/week. (Level 1+)

Intravenous iron studies in children

In a 6-month study[84] (n=40) children below 16 years of age received epoetin to target Hct ≥30% and i.v. iron dextran administered as a maintenance dose of 1 mg/kg/week following a weight-based loading dose. This 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 in children <16 years old receiving epoetin[372] randomised patients to concomitant treatment with eight consecutive intravenous infusions of either 1.5 mg/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 numbers 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[207]. 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 seven patients, pain during injection in 31 patients, pain after injection in nine patients, with/without bruising, nausea/GI symptoms in three patients, lethargy in four patients, and light-headedness in three patients. (Level 3)

A cohort study[105] (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 with 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 0 to 6 months, 6 to 12 months and 12 to 18 months was estimated. No significant association was found between mortality and any level of iron dosing >0 to >1,800 mg over 6 months. (Level 2+)

Oral iron studies

One study[211] 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 two 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[379] 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+)

6.14.4 Health economics methodological introduction

Six studies were appraised[45,94,228,274,312,331] and one study met quality criteria[94]. Three of the studies did not report unit costs, total costs or doses adequately[45,228,312] One study was excluded because of potential bias by physician adjustment of the epoetin dose in a before and after design[274]. One study[331] was excluded as cost-savings were not based on evidence.

6.14.5 Health economics evidence statements

One study found iron dextran did not reduce the average dose of ESA in 33 patients but improved the number of patients with 'successful treatment' (10 vs 27). Successful treatment was defined as

Hct 33–36%, TSAT >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[94]. No sensitivity analysis was performed.

6.14.6 From evidence to recommendations

The published evidence was very limited in peritoneal dialysis and predialysis 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.

Caution is required because of the potential side-effect profile (particularly anaphylaxis) when administering both test and maintenance doses of iron. The GDG considered additional retrospective studies of adverse events in patients receiving intravenous iron to inform the recommendations:

- Baillie et al[30] investigated tens of millions of 100mg dose equivalents (the exact sample size is not given in the paper) from the American Food and Drug Administration (FDA) 'freedom of information surveillance database'. They considered all adverse events between January 1997 and September 2002 and found rates per million 100mg dose equivalents of 29.2 for iron dextran, 10.5 for sodium ferric gluconate and 4.2 for iron sucrose (which had the lowest rates for all clinical categories of adverse event).
- Chertow et al[64,65] investigated 30,063,800 doses in FDA data from 2001 to 2003 and found significantly lower rates among people who received sodium ferric gluconate or iron sucrose, compared with those who received higher molecular weight iron dextran. Rates of 'life-threatening' events per million doses were 11.3 for higher molecular weight iron dextran, 3.3 for lower molecular weight iron dextran, 0.9 for sodium ferric gluconate, and 0.6 for iron sucrose.
- Fishbane et al[112] investigated all patients (n=573) receiving intravenous iron dextran at any of four USA haemodialysis centres between July 1993 and June 1995 and found 27 patients (4.7%) had related adverse events. History of drug allergy (OR 2.4, p=0.03) and multiple drug allergy (OR 5.5, p<0.001) were found to be significant risk factors for adverse events.
- Fletes et al[114] investigated the Fresenius Medical Care North America (FMCNA) clinical variance reports from October 1998 to March 1999 for iron dextran only and found an adverse event rate of 196.1 per million doses. The study reported higher rates in patients receiving higher molecular weight iron dextran, but this was not statistically significant.
- Walters and van Wyck[370] investigated 1,066,099 doses of intravenous iron dextran from the Gambro Healthcare US database between January 1999 and April 2000. They found a rate of 316.1 adverse events per million doses for all severities, and reported in detail on seven patients who had adverse events requiring resuscitation, all of whom were receiving test doses or first therapeutic doses. Significance testing to compare molecular weights of iron dextran was only reported for these seven patients.

Adverse event rates for intravenous iron are very low for both preparations in use in the UK (circa 3.3 events per million doses for low molecular weight iron dextran, and 0.6 per million doses for iron sucrose), and the GDG therefore did not distinguish between them in the recommendation.

The GDG acknowledged the cost-effectiveness evidence of predialysis 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 in all future randomised controlled trials would be useful, especially in predialysis patients.

6.14.7 Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.15 Iron therapies

This section was updated and replaced in 2021. See www.nice.org.uk/guidance/ng203/evidence for the 2021 evidence reviews.

1

6.16 ESAs: monitoring iron status during treatment [2006]

6.16.1 Clinical introduction

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?

6.16.2 Clinical methodological introduction

A literature search identified four studies consisting of a RCT[40], a cohort study[161], a prospective longitudinal study[300] and a prospective longitudinal study in children[347].

One study[163] did not meet quality criteria and was therefore excluded from the evidence statements.

Notable aspects of the evidence base were:

- In the study comparing TSAT 20–30% and 30–50%[40], achieved TSAT levels were 27.6% and 32.6% in the respective groups at the end of the 6-month study period.

6.16.3 Clinical evidence statements

Serum ferritin

Haemodialysis patients

Intravenous iron supplementation which led to an increase in mean ferritin to 395 ± 206 mg/100 ml (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[347]. (Level 3)

In a 24-month study (n=396)[300] Hb was maintained at a median level of 11.3 to 11.8 g/dl and median epoetin dose decreased to 72 (inter-quartile range 33–134) (p<0.001) when compared with baseline, when patients with serum ferritin <500 ng/ml were treated with concomitant i.v. iron sucrose regimen. (Level 3+)

Transferrin saturation (TSAT)

Haemodialysis patients

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 with the 20–30% group (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[40]. (Level 1+)

Percentage of hypochromic red cells (%HRC)

Haemodialysis patients

In an 8-week study whereby patients stratified by baseline %HRC 0–3%, 4–9% and ≥10% received a fixed epoetin dose and i.v. 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≤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)[161]. (Level 2+)

6.16.4 Health economic methodological introduction

Three studies were appraised[40,149,312] and two met quality criteria[40,149]. The study that did not meet quality criteria estimated cost-savings based on average reduced EPO dosages[312]. However, with no inclusion of the prices used, the costing was not sufficiently transparent to warrant inclusion.

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[40].

One American study was a cost analysis of ESAs using percent reduction of urea (PRU) as an index of dialysis adequacy and transferrin saturation as a measure of iron stores. The study investigated two comparisons: the total dose of ESA 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 ESA administered during the 4-week study to the 20 patients with the highest PRU to the 20 participants with the lowest PRU[149].

6.16.5 Health economic evidence statements

The study estimated intravenous iron dextran saves approximately $109 per month or $1,308 per year per patient when maintaining the TSAT between 30 and 50% (n=23) (vs 20 to 30% in control group; n=19)[40]. Cost difference between the intervention and control group was statistically significant by the third month of study and remained significant until the end of the study at 6 months (p<0.02)[40].

At $10 per 1,000 units of ESA, it costs $45 (10.2%) more per month per patient in the 20 patients with the lowest transferrin saturation compared with the 20 patients with the highest transferrin saturation[149].

6.16.6 From evidence to recommendations

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[2].

6.16.7 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

7 Monitoring treatment of anaemia of CKD

7.1 Monitoring iron status [2006, 2015]

7.1.1 Clinical introduction

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, ie initial correction of anaemia or maintenance of target range of haemoglobin, the frequency and mode of iron supplementation, CKD status (haemodialysis patients have an unavoidable 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 (for example, 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

A comprehensive literature search identified a cohort study[42].

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 73: Time profile of intermittent i.v. iron dextran dosing regimen (n=14) (Level 2)

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

Monitoring after single iron dose

Haemodialysis patients

Table 74: Time profile of single dose i.v. iron dextran 50 mg or 100 mg (n=16) (Level 2+)

	T=0	Time averaged over 2 weeks
TSAT (%)	Mean 34.6 ± 3.1 (n=16)	35.5 for 50 mg group (n=8) 36.7 for 100 mg group (n=8)
	T=0	
Ferritin (ng/ml)	231 ± 29 (n=16)	T=1 week, 297 ± 44 (n=16)
		T=2 weeks, 276 ± 35 (n=16)
	T=0	**Time averaged over 2 weeks**
TIBC (µg/ml)	Not reported	No change (data not reported)

7.1.4 From evidence to recommendations

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

The current recommendations can be found at www.nice.org.uk/guidance/ng203

7.2 Monitoring haemoglobin levels [2006]

7.2.1 Clinical introduction

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, comorbid 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 months 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[181]. 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

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

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 Recommendation

- **The current recommendations can be found at www.nice.org.uk/guidance/ng203**

7.3 Detecting ESA resistance [2006]

7.3.1 Clinical introduction

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

A literature search identified a case series[57] and a cohort study[345].

Five studies[34,136,168,314,324] did not meet quality criteria and were therefore excluded from the evidence statements.

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

In a study of patients predominantly receiving subcutaneous epoetin alfa, 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[57]. (Level 3)

Aluminium toxicity

Haemodialysis patients

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 ($r=-0.476$, $p=0.03$)[345]. (Level 2+)

7.3.4 From evidence to recommendations

In 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.

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[4]. It was agreed to suspect resistance when a patient does not achieve the target Hb level after receiving an epoetin dose more than 300 U/kg/week s.c. (approximately 20,000 units/week) or equivalent or 1.5 mg/kg darbepoetin alfa s.c. or i.v. (approximately 100 mg/week) or has a continued need for the administration of high doses of ESAs to maintain the target Hb level.[4] It was noted that 300 U/kg/week is used as this value is two standard deviations above 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 (eg intercurrent illness or other causes of chronic bleeding).

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 erythropoietin. This has since been addressed by using a fluoro-resin coating, which forms a barrier between the rubber stopper and erythropoietin in some pre-filled syringes. The evidence presented specifically addressed PRCA induced by sensitisation to erythropoietin and demonstrated that the inhibition of the erythroid cells was correlated with the presence of anti-erythropoietin antibodies[57].

The GDG noted that the issue of aluminium toxicity was of clinical importance but the incidence is now very rare. 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). However, 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[345] did not report either the use of aluminium-based phosphate

binders or whether any water purification system was being used. The GDG 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

- **The current recommendations can be found at www.nice.org.uk/guidance/ng203**

7.4 Managing ESA resistance [2006]

7.4.1 Clinical introduction

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 1,000 patients years on ESA while on dialysis.[172] Fifty-seven of 1,677 patients with incident end stage renal disease in the NECOSAD-2 study had an inadequate ESA response. Table 75 shows the various causes identified.

Table 75: Possible causes for ESA resistance from the NECOSAD-2 study (n=57)

Causes for inadequate ESA response	Number*	Causes for inadequate ESA response	Number*
Infection/inflammation	41	Haemolysis	0
Blood loss	16	Pure red cell aplasia	1
Hyperparathyroidism/aluminium toxicity	10	Malignancy	7
Haemoglobinopathy	2	Graft/shunt problems	14
Folate/vitamin B12 deficiency	1	Operation	8
Multiple myeloma/myelofibrosis/myelodysplastic syndrome	6	Suspected noncompliance	9
Malnutrition	5	Medication (≥bone marrow suppress)	4
Inadequate dialysis	2	Unknown	2
* Some patients fell into more than one category (ie there was more than one possible cause for their inadequate ESA response).			

7.4.2 Methodological introduction

The literature search identified three studies: a 2-part study with a prospective cohort group and a subsequent before and after study in a subgroup[384], a retrospective case series[367] and a before and after study[72].

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

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[384]. 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+)

In addition, concurrent treatment with desferrioxamine in this group led to a mean Hb rise when compared with previous treatment with epoetin only ($p<0.01$)[384]. (Level 3)

Reduced T-cell production of inflammatory markers TNF-α and IFN-γ with low dose pentoxifylline

Patient population not specified

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-α ($p=0.0007$) and IFN-γ ($p=0.0002$) 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-α production ($rs=0.7145$, $p=0.0118$), however, no correlation was found between change in Hb and IFN-γ ($rs=0.4406$, $p=0.1542$)[72]. (Level 3)

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

Not on dialysis, haemodialysis and peritoneal dialysis patients

In a group of patients with epoetin-induced PRCA (n=43 epoetin alfa ± epoetin beta or darbepoetin and n=4 epoetin beta exclusively), 37 patients received treatment which consisted of one treatment (n=26), two consecutive treatment regimens (n=10) or five different regimens (n=1). Of these, 29 patients recovered (ie 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 in the Table 76.

Table 76: Summary data from Verhelst (2004)290 (Level 3)

PRCA treatment	n	Number of patients who recovered	Time before recovery (months)	Follow-up (months)
Corticosteroids alone (n=14) ± high dose i.v. immunoglobulins	18	10 (56%)	1†, 2†, 2†, 3†, 3†, 3†, 3†, 3†, 6†, 18†	3, 3, 3, 3, 5†, 13†, 20, 30†
High dose i.v. immunoglobulins alone	9	1 (11%)	3†	3, 3, 4, 4, 4, 9, 10†, 19
Corticosteroids + cyclophosphamide	8	7 (87%)	1†, 2, 2, 3†, 4, 5, 7	3
Ciclosporin	6	4 (67%)	1†, 1†, 1†, 1	3, 9†
Kidney transplant*	6	6 (100%)	<1†, <1†, <1†, <1†, <1, <1	–
Antibodies to CD20	2	0	–	3†, 3
Corticosteroids + high dose i.v. immunoglobulins + plasma exchange	1	1 (100%)	3†	–
Mycophenolate motefil	1	0	–	12

Note: for patients who did not recover, follow-up was length of time between start of treatment and last visit or start of new treatment.

PRCA treatment	n	Number of patients who recovered	Time before recovery (months)	Follow-up (months)
† Received only 1 kind of treatment.				
* Received induction treatment followed by triple immunosuppressive therapy.				

7.4.4 From evidence to recommendations

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.

The GDG noted that with regard 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.

With regard 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-α and IFN-γ) by T-cells[72]. 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.

The GDG reviewed evidence on the treatment of ESA-mediated PRCA. The GDG felt this was a specialised area with few annual cases. Because of this, the GDG acknowledged that the treatment of this condition was not fully established and that the most up-to-date information was available online and was written by the PRCA Global Scientific Advisory Board[289] 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 the GSAB suggested ciclosporin as the treatment of choice.

7.4.5 Recommendations [2006, Updated 2011]

The current recommendations can be found at www.nice.org.uk/guidance/ng203

7.5 Treatment of ESA resistance [2015]

7.5.1 Introduction

The use of ESA's in the treatment of renal anaemia is well established. Their success in the improvement of the patients' physical health and quality of life, whilst also reducing the necessity of blood transfusion is well known. In short, ESA usage in the renal setting has delivered real positive impact upon a majority of patients who use them.

However, whilst the efficacy of these medications is recognised, resistance is not unknown. The efficacy of an ESA can be restricted for a number of reasons. Contributing factors that might lead to ESA resistant anaemia include:

- Iron deficiency
- Vitamin B12 and/or folic acid deficiency

- Active blood loss
  - during dialysis
  - chronic blood loss
- Haematological disorders
- Pure red cell aplasia
- Severe hyperparathyroidism
- Aluminium toxicity
- Chronic infection or inflammation including :
  - Low-grade vascular access infection
  - connective tissue disease
  - atherosclerosis
- Drug-related anaemia (including drugs exacerbating blood loss)
- Poor concordance

Continuing poorly managed or undiagnosed ESA resistance will have direct negative consequences for the patient along with increased economic burden for the health economy. If ESA resistance is recognised early, problems such as long-term blood transfusion dependence, increasing cardiac morbidity and subsequent reduced quality of life might be avoided. The GDG wished to ascertain the optimal strategy for managing anaemia in people with chronic ESA resistance to provide clear, sound direction for clinicians.

7.5.1.1 Review question: In people with chronic ESA-resistant anaemia of CKD, what is the clinical and cost effectiveness of treating with high-dose ESA compared with blood transfusion?

For full details see review protocol in Appendix C.

Table 77: PICO characteristics of review question

Population	Adults, children and young people with anaemia of CKD suspected of being ESA-resistant, including those treated with haemodialysis, peritoneal dialysis, not receiving dialysis and post-transplant.
Intervention/s	High-dose ESA +/- transfusion
Comparison/s	• Transfusion alone • Transfusion +/- standard dose ESA
Outcomes	Critical (treatment-related outcomes) • Improvement in haemoglobin (Hb) levels (mean Hb in the course of the study) • Number of units transfused • Average ESA use per patient Important • Morbidity, including: ○ hospitalisation - admission to hospital (might not always be reported) ○ HRQOL • Mortality – 6 months and 1 year (if see a change earlier than 6 months it is unlikely to be due to the strategy used)
Study design	Initially look for RCTs. If none identified, we will look for prospective cohort studies

7.5.2 Clinical evidence

No relevant clinical studies (RCT or observational) comparing the use of high dose ESA to blood transfusion were identified.

7.5.3 Economic evidence [2015]

Published literature

No relevant economic evaluations were identified.

Unit costs

In the absence of relevant economic evidence unit costs were provided to aid GDG consideration of cost-effectiveness. Costs are estimated over a 6 month period, and only include the upfront costs of ESA and transfusion; additional costs, such as those which may arise due to adverse events, are not included.

The GDG provided estimates of the doses of ESA required for the high-dose ESA regimen (see Table 78). Iron would also be required as part of the high-dose ESA strategy, therefore, the GDG also provided an estimate of the required weekly dose of iron. Note that the costs of ESA and iron are subject to local variation, and prices paid are likely to be lower than those reported in national sources. The cost of high-dose ESA is therefore calculated using the lowest cost preparation in the BNF[160] (Binocrit), and it is expected that this is still an overestimate. Similarly, the price of iron is based on the BNF price for Venofer, but this is also likely to be an overestimate. The costs for these are presented in Table 78.

The cost of transfusion is estimated in Table 79. The units of blood given per transfusion, and number of transfusions over a 6 month period, are based on GDG estimates; cost sources are reported in Table 79. Note that the amount of healthcare professional time required was considered to be highly variable between patients (rather than between strategies), and therefore, has not been included in the cost calculations for high dose ESA or for transfusion.

Table 78: Cost of high-dose ESA

Component	Dose per week	Cost per week[a]	ESA cost per 6 months	Total cost per 6 months (ESA + Iron)
ESA (subcutaneous)	20,000 IU	£102	£2,647	**£3,979**
ESA (IV)	30,000 IU	£153	£3,971	**£5,302**

(a) BNF 66[160]
(b) Weekly dose 100 mg; cost per week £51.20[160]; cost per 6 months £1,331

Table 79: Cost of transfusion

Component	Unit cost	Quantity	Cost per transfusion	Cost per 6 months[a]
Red blood cells	£122 per unit[b]	2 units[c]	£244	£1,465
Consumables	£13[d]	1	£13	£80
Total			£257	**£1,545**

(a) Based on GDG estimate of 6 transfusions over 6 months
(b) NHS BT[253]
(c) GDG assumption

(d) Agrawal and colleagues (2006).[11,11] Nurse time estimate includes time required for patient assessment, patient safety checks, transfusion preparation and transfusion. Consumables estimate includes all disposables used for each transfusion procedure as noted by a research nurse observing transfusions.

Table 78 and Table 79 show that, based on the assumptions outlined above, treatment with high-dose ESA appears to be more costly than transfusion over a 6 month period, in people with ESA resistant anaemia.

7.5.4 Evidence statements

Clinical

No relevant clinical evidence was identified.

Economic

No relevant economic evaluations were identified.

7.5.5 Recommendations and link to evidence [2015]

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG discussed the relative values of different outcomes and agreed that the treatment-related outcomes were the critical for decision making. These included improvement in Hb levels, number of units transfused and average use of ESA per patient. Other outcomes were also considered as important for decision making and these include length of hospital stay, in hospital mortality at 6 months and 1 year, and health-related quality of life (HRQoL).
Trade-off between clinical benefits and harms	The GDG discussed the clinical and economic implications of high-dose ESA and transfusion. It was noted that the adverse event profiles differ between strategies, which will most likely lead to further differences in costs and health-related quality of life. For blood transfusions, the GDG considered the possibility of human leukocyte antigen (HLA) sensitisation, blood borne virus infection and transfusion reactions (for example, pyrexia or itch, or more severe allergic reactions which might require admission). High ESA dose, on the other hand, may be associated with higher overall mortality and cardiovascular complications. The majority of these adverse events would most likely have cost implications and may adversely affect quality of life. The GDG discussed the importance of adopting an individualised strategy for each patient according to their clinical needs, both short term and in the future. This is particularly relevant in certain groups of patients, for example, patients with particular cultural or religious beliefs. Likewise, one should consider anticipated life expectancy given the significant comorbidities many of these patients have. In the absence of evidence, the GDG drafted recommendations based on consensus which took into account take into account the above considerations.
Economic considerations	No economic evidence was identified. Calculations of unit costs for high-dose ESA and transfusion revealed that, based on list prices, high-dose ESA is more costly than transfusion for treatment of ESA-resistant anaemia over a 6 month period. However, the GDG noted that in reality the costs of ESA are likely to be lower than the list prices because of negotiated purchasing arrangements locally.

	In addition, the cost calculations only included the upfront costs of each strategy, and did not consider the health benefits or downstream resource implications. The GDG noted that with blood transfusions, there is possibility of HLA sensitisation (meaning the chances of an unsuccessful transplant are increased), as well as the possibility of contracting blood borne virus', or experiencing transfusion reactions (for example, pyrexia or itch, or more severe allergic reactions which might require admission). High-dose ESA, on the other hand, may be associated with higher overall mortality and cardiovascular complications. The majority of these adverse events would most likely have cost implications and may adversely affect quality of life. Unfortunately, no clinical evidence was found; therefore, it is unclear which the most clinically effective strategy is. The GDG also noted that in some scenarios a combination of high-dose ESA and transfusion may be required. Overall the GDG felt that, in the absence of clinical evidence, they were unable to draw any firm conclusion on cost-effectiveness or quality of life. The recommendations made are considered current best practice, and are not considered likely to lead to a substantial increase in resource use.
Quality of evidence	No evidence was identified for this review. The recommendations are based on the consensus expert opinion of the GDG members.
Other considerations	The GDG noted the lack of evidence in this area. They observed that a typical patient with CKD and ESA-resistant anaemia will be a haemodialysis patient, often with multiple interconnecting factors contributing to the anaemia, other than end stage renal disease (ESRD). Usually, the patient will be on a high ESA dose, yet also require periodic or ad hoc transfusion(s) for symptomatic anaemia. Such factors include infection, suboptimal dialysis adequacy and temporary dialysis access. They noted that dialysis should be optimised as far as possible, including both access and dialysis adequacy. The recommendations apply to both adults and children. The GDG were aware that ESA resistance had already been defined in recommendations made in previous versions of this guideline (see recommendation 49).The GDG noted that this definition does not cover Mircera, but did not define ESA resistance in this circumstance as its role was not being covered in the guideline. The GDG also discussed the changing risk benefit ratio in patients close to end of life care. It was noted that quality of life may be more important than achieving target Hb levels and due consideration should be given to this when deciding on the need for a blood transfusion. The GDG did not feel a recommendation was necessary, as this decision would be made on an individual case by case basis. In describing the management of ESA-resistant anaemia, the GDG decided not to recommend one strategy or the other for every patient, but felt that their recommendations should emphasise that providing advice at an individual level (according to risk and benefits for each patient) would be more appropriate. Specific considerations discussed by the GDG with respect to each of the above recommendations are outlined below: **Recommendation 1:**

Currently ESA-resistant anaemia is a diagnosis of exclusion. The GDG agreed by consensus that the following causes or contributing factors should be excluded before ESA resistant anaemia is 'diagnosed.' Not all described causes of anaemia in ESRD are listed below, but commoner causes are highlighted:

- iron deficiency (the diagnosis of iron deficiency is covered elsewhere in the guideline (see Chapter 4.3) The investigation for causes of possible iron deficiency in CKD is beyond the scope of the guideline.)
- vitamin B12 and/or folic acid deficiency
- active blood loss:
  - during dialysis
  - chronic blood loss
- haematological disorders (overt or more subtle)– including myelodysplasia
- pure red cell aplasia
- severe hyperparathyroidism
- aluminium toxicity
- chronic infection or inflammation – including:
  - low grade access infection
  - connective tissue disease
- drug-related anaemia – including ACE inhibitors and drugs exacerbating blood loss (aspirins or anticoagulants)
- non-concordance

The GDG were aware that myelodysplastic disorders should be considered as a cause of refractory or ESA-resistant anaemia, when other causes discussed above are excluded. This will require referral to a haematology service when appropriate. It was noted that in the usual experience of the GDG, such patients would typically be referred after being seen by a renal specialist. The GDG noted that this is usual practice. However, in people with anaemia of chronic kidney disease, only a very small number of patients will present with myelodysplastic disorders and will need referral to a haematologist; therefore, the need for such referral is rare.

Recommendations 2 and 3:

The GDG felt that blood transfusion may provide a transient correction of anaemia in patients with ESA hyporesponsiveness. However, the GDG noted that the risk of sensitisation with a blood transfusion should be taken into particular consideration in patients likely to receive a renal transplant. This is a major concern in children and young people who may need more than one transplant in their lifetime. The GDG felt that it would be important to discuss the risks and benefits of any transfusion with the patient and/or their carer before deciding the treatment option.

The GDG emphasised that there are various factors to be taken into consideration when deciding to transfuse an anaemic patient with CKD, not just achieving a target Hb level. In particular the GDG noted that the decision to transfuse should be informed by consideration of symptoms, usual exercise capacity, other comorbidities that may limit exercise capacity, and the person's quality of life. Thus, the GDG felt that transfusion should not 'automatically' happen if the Hb falls below an arbitrary level.

Recommendation 4:

The GDG noted that a trial of ESA cessation may be worthwhile only under very defined circumstances for example:

- A patient, typically on dialysis, with ESA-resistant anaemia, using a high dose of ESA therapy, yet still requiring frequent transfusion to maintain Hb.
- The patient is otherwise 'stable' and receiving adequate dialysis, without

	intercurrent illness, such as infection (discussed elsewhere in the guideline in section 6.12). • All causes of ESA resistance have been considered and excluded. The GDG felt that under these circumstances, it would first be sensible to observe the rate of transfusion over a period of time whilst on high-dose ESA. Thereafter, the effect of stopping the ESA on transfusion usage could be determined after a further period. The GDG agreed by consensus that each period of observation should be between 1 and 3 months and individualised according to patient circumstances. The GDG also noted that ESA resistance is not a fixed phenomenon and patients may respond differently to ESA therapy at different times, and this has an effect on red cell transfusion usage. Therefore, in stable ESA-resistant CKD patients who have had their ESA withdrawn over months, consideration should be given to a planned ESA reintroduction, particularly if any causes of ESA resistance have been addressed. The benefits could then be reassessed, particularly with regards to transfusion usage. In the absence of any evidence, the recommendations were based on the consensus expert opinion of the GDG members. The GDG also noted that this topic area would benefit from further research and formulated research recommendations aimed at understanding factors affecting ESA resistance and evaluating efficacy of blood transfusions in comparison to high dose ESA to address ESA resistance.(see section 7.5.6)

7.5.6 Research recommendation

Research question:

In people with chronic ESA-resistant anaemia of CKD, what is the clinical and cost-effectiveness of treating with high-dose ESA compared with blood transfusion?

Why this is important

People with ESA hyporesponsiveness show evidence of increased morbidity and mortality compared with those who respond well to ESA therapy. Poor response to ESA therapy during the haemodialysis treatment period is thought to be associated with worse post-transplant long-term outcomes, including increased all-cause death and higher risk of graft failure. [224,259,340] Little is known about the potential risks of maintaining people with CKD on high doses of ESA therapy while they are waiting for a kidney transplant. It is unclear whether high-dose ESA should be continued in people with ESA resistance in an attempt to limit the number of blood transfusions, or whether people should stop ESA treatment and be treated with transfusions alone. The adverse effects differ between the strategies and are likely to have implications for both cost and quality of life.

Further research is needed to understand the clinical and cost-effectiveness of these 2 strategies. Long-term prospective observational or matched case-controlled studies are needed to assess the relative safety of large-dose ESA versus no ESA, with or without blood transfusions, on long-term patient and graft survival.

Research question:

What is the most effective type of intervention to treat haemodialysis patients with ESA-resistant anaemia?

Why this is important

Around 5% to 10% of patients with end-stage renal disease show resistance to ESAs. ESA hyporesponsiveness in chronic haemodialysis patients may be associated with increased morbidity and mortality.[259] In addition, pre-transplantation ESA hyporesponsiveness is thought to be associated with increased kidney allograft failure and patient mortality.[74] Studies have shown that immunosuppressants, anti-oxidants, anti-cytokine therapies and high-flux membranes vary in how much they improve responsiveness to ESA therapy, but all the studies used a small sample size. There is inadequate evidence identified from available literature to inform recommending any intervention to improve ESA responsiveness.[28]

Adequately powered randomised controlled trials are needed to establish the safety and efficacy of interventions to improve responsiveness to ESA therapy.

8 Glossary

All recommendations and evidence in 2015 follow the new units of haemoglobin (Hb) measurement, that is, grams/litre as outlined in the latest information sheet for laboratories on change in haematology units [276] The recommendations from CG39 and CG114 that make reference to Hb measurement have been amended to reflect this. However, the text in individual chapters in support of the recommendations has not been amended.

8.1 Guide to assessment scales [2015]

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	A quality of life scale developed and validated specifically for people with renal disease.
Short Form 36 (SF-36)	The SF-36 assesses functioning and well-being in chronic disease. Thirty-six items in eight domains are included, which cover functional status, well- being, and overall evaluation of health.
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 six categories: no pain, hardly any pain, mild pain, moderate pain, severe pain, unbearable pain. Patients tick the appropriate category on a questionnaire

8.2 Stages of CKD [2015]

Table 80: Kidney Disease Improving Global Outcomes GFR categories

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	>90	Normal or high
G2	60–89	Mildly decreased[a]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: *CKD, chronic kidney disease; GFR, glomerular filtration rate*

Note: *Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 3: 1–150.*

(a) Relative to young adult level.

Table 81: Kidney Disease Improving Global Outcomes ACR categories

ACR category	ACR (mg/mmol)	Terms
A1	<3	Normal to mildly increased
A2	3–30	Moderately increased*
A3	>30	Severely increased**

Abbreviations: *ACR, albumin:creatinine ratio; CKD, chronic kidney disease*

Note: *Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 3: 1–150.*

(a) Relative to young adult level
(b) Including nephrotic syndrome (ACR usually >220 mg/mmol)

8.3 Abbreviations and Definitions of terms [2015]

ACKD	Anaemia of chronic kidney disease
AUC	Area under the curve
bd	Twice daily
CAPD	Continuous ambulatory peritoneal dialysis
CCr	Creatinine clearance
CHr	Reticulocyte haemoglobin content
CI	Confidence interval
CKD	Chronic kidney disease
DALYs	Disability-adjusted life years
DM	Diabetes mellitus
DS	Diagnostic study
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
EQ-5D	EuroQol-5 Dimensions
ESA	Erythropoiesis stimulating agent
FBC	Full blood count
FID	Functional iron deficiency
GDG	Guideline development group
GI	Gastrointestinal
GFR	Glomerular filtration rate
GPP	Good practice point
Hb	Haemoglobin
Hct	Haematocrit
HD	Haemodialysis
HR	Hazard ratio
HRC	Hypochromic red cells
HYEs	Healthy year equivalents
ICER	Incremental cost-effectiveness ratio
IP	Intraperitoneal
IU	International units
i.v.	Intravenously
LVH	Left ventricular hypertrophy
MCV	Mean corpuscular volume
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence

NMB	Net monetary benefits
NSF	National service framework
PD	Peritoneal dialysis
PRCA	Pure red cell aplasia
PTX	Parathyroidectomy
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RES	Reticuloendothelial system
ROC	Receiver-operator curve
RR	Relative risk
SAE	Serious adverse event
s.c.	Subcutaneous
s.c.r	Serum creatinine
SE	Standard error
SF	Serum ferritin
sTfR	Serum/Soluble transferrin receptor
TIBC	Serum total iron binding capacity
tds	Three times daily
TSAT	Transferrin saturation
WMD	Weighted mean difference
ZPP	(Erythrocyte) zinc protoporphyrin

8.4 Definition of terms [2015]

Absolute iron deficiency	Depletion in iron body stores.
Adverse events	A harmful, and usually relatively rare, event arising from treatment.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT, and potential bias that may result.
Anaemia coordinator	A healthcare professional who is a central point of contact for patients with ACKD – see recommendation 28 in section 6.5.3 for details.
Area under the curve	Overall summary of performance or diagnostic accuracy of an index test (compared against a reference standard).
Audit	See 'clinical audit'.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before and after study	See 'observational study'.
Bias	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.
Blinding (masking)	A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions that have been allocated.

Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.
Case-control study	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.
Class of recommendation	All recommendations are assigned a class (A, B, C, D, A(DS), B(DS), C(DS), or D(GPP)) according to the level of evidence the recommendation is based on (see 'level of evidence').
Clinical audit	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.
Clinician	In this guideline, the term clinician means any healthcare professional.
Cochrane review	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.
Cohort study	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.
Concordance	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.
Confidence interval	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.
Cost-effectiveness analysis	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.
Cost-effectiveness model	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.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life years (QALYs).
Cycling	See 'haemoglobin cycling'.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast see Probabilistic analysis.
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.

Diagnostic study	Any research study aimed at evaluating the utility of a diagnostic procedure.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Erythropoiesis	Red blood cell production.
Evidence-based healthcare	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
False negatives	Incorrect negative test result – number of people diagnosed with iron-deficiency anaemia with a negative index test result.
False positives	Incorrect positive test result – number of people diagnosed as not having iron-deficiency anaemia with a positive index test result.
Follow up	An attempt to measure the outcomes of an intervention after the intervention has ended.
Functional iron deficiency	Inadequate iron mobilisation, which is incapable of meeting demands of erythropoiesis.
Generalisability	The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.
Gold standard	See 'reference standard'.
Good Practice Point	Recommended good practice based on the clinical experience of the Guideline Development Group.
Grade of recommendation	See 'class of recommendation'.
Guideline development group (GDG)	An independent group set up on behalf of NICE to develop a guideline. They include healthcare professionals and patient and carer representatives.
Haematocrit	Relative volume of blood occupied by red blood cells.
Haemoglobin cycling	Fluctuation of haemoglobin levels which may vary from patient to patient.
Hazard ratio	A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.
Heterogeneity	In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.
Homogeneity	In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.
Inclusion criteria	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The cost of one alternative less the cost of another.

Incremental cost-effectiveness ratio (ICER)	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
Intention-to-treat analysis (ITT analysis)	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.
Level of evidence	A code (for example, 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.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	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.
Methodological limitations	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.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
National Health Service	This guideline is written for the NHS in England and Wales.
National Institute for Health and Clinical Excellence	NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
Negative likelihood ratio	How many times more likely a negative test result occurs in patients with compared with those without iron-deficiency anaemia.
Negative predictive value	The proportion of people with a negative test result who do not have the disease.
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost compared with a comparator intervention. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NB for an intervention is calculated as: (£20,000 x mean QALYs) – mean cost. The most cost-effective option is the treatment with the highest NMB.
Observational study	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.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.
Outcome	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.
p-values	The probability that an observed difference could have occurred by chance. A p-value of less than 0.05 is conventionally considered to be 'statistically significant'.

Placebo	An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.
Positive likelihood ratio	How many times more likely a positive test result occurs in patients with compared with those without iron-deficiency anaemia.
Positive predictive value (PPV)	The proportion of people with a positive test result who actually have the disease.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Pretest probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast see Deterministic analysis.
Pure red cell aplasia	Transitory arrest of erythropoiesis.
Quality of life	Refers to the level of comfort, enjoyment, and ability to pursue daily activities.
Quality-adjusted life year (QALY)	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.
Randomisation	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.
Randomised controlled trial	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.
Reference standard (or gold standard)	An agreed desirable standard, for example a diagnostic test or treatment, against which other interventions can be compared.
Relative risk	An estimate for the number of times more likely or less likely an event is to happen in one group of people compared with another, based on the incidence of the event in the intervention arm of a study, divided by the incidence in the control arm.
Sample size	The number of participants included in a trial or intervention group.
Sensitivity (of a test)	The proportion of people classified as positive by the gold standard, who are correctly identified by the study test.
Sensitivity analysis	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.
Single blind study	A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.
Specialist	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
Specificity (of a test)	The proportion of people classified as negative by the gold standard, who are

	correctly identified by the study test.
Stakeholder	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
State transition model	See Markov model.
Statistical power	In clinical trials, the probability of correctly detecting an underlying difference of a pre-specified size 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 correctly detected as statistically significant, though they may not be clinically significant.
Statistical significance	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Systematic review	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.
Test and Treat RCTs	'Test and treat' randomised controlled trials refer to study designs in diagnostic studies which involve randomised comparisons of two diagnostic tests (one being the index test and the other the reference standard) followed by identical treatments interventions based on the results of the diagnostic tests. The outcomes of the study are acknowledged to be clinically important consequences of the tests of diagnostic accuracy.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model, this is the probability of moving from one health state to another over a specific period of time.
True negatives	Correct negative test result – number of people diagnosed as not having iron-deficiency anaemia with a negative index test result.
True positives	Correct positive test result – number of people diagnosed with iron-deficiency anaemia with a positive index test result.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).
Washout period	The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.
Withdrawal	When a trial participant discontinues the assigned intervention before completion of the study.

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