Background information

Guideline issue date: CG 39 2006
2 year review: CG39 2008 (first review)
5 year rapid update: CG114 Feb 2011 (superseded CG39)
5 year review: CG114 Nov 2011 (second review)

National Collaborating Centre: National Collaborating Centre for Chronic Conditions

1. Consideration of the evidence

Literature search

From a high-level randomised control trial (RCT) search, new evidence was identified related to the following clinical areas within the guideline:

- **Management of anaemia**
  - Nutritional supplements
  - Androgens
  - Patient centred care

- **Assessment and optimisation of erythropoiesis**
  - Benefits of treatment with erythropoiesis-stimulating agents (ESAs)
- Monitoring treatment of anaemia of CKD

Through this stage of the process, a sufficient number of 78 studies relevant to the above clinical areas were identified from the high level RCT to allow an assessment for a proposed review decision and are summarised in table 1 below.

From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, as well as the high-level RCT search, an additional focused literature search was also conducted for the following clinical area:

- The risk and benefits of correcting anaemia in patients with CKD and a malignancy.

The results of the focused searches are also summarised in table 2 below. All references identified through the high-level RCT search, initial intelligence gathering and the focused search can be viewed in Appendix 1.
Table 1. Summary of articles from the high level RCT search

<table>
<thead>
<tr>
<th>Clinical area 1: Management of anaemia</th>
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<tr>
<td><strong>Clinical question</strong></td>
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<tr>
<td>Related clinical questions from the guideline</td>
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<tr>
<td>What is the benefit of vitamin C, vitamin E, folic acid, carnitine or glutathione supplementation in the treatment of anaemia due to chronic kidney disease?</td>
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<tr>
<td>What is the benefit of androgens in the treatment of anaemia</td>
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due to chronic kidney disease? What are the patient preferences and experiences when receiving ESAs for the treatment of ACKD?

**Relevant section of guideline**

5.5, 5.7

**Recommendations**

R15, R16, R21

<table>
<thead>
<tr>
<th>Due to chronic kidney disease?</th>
<th>What are the patient preferences and experiences when receiving ESAs for the treatment of ACKD?</th>
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| Mobilization from its tissue stores or through antioxidant effects | **Androgens**

Three RCTS published just after the final evidence search for the original guideline in 2005 were identified. Two studies indicated that adjunct androgen therapy did not show any clinical benefit whereas one RCT indicated some efficacy in a subgroup of male patients who were over 50 years old.

**Patient centred care**

Three studies, one in paediatric patients, were identified that had specifically addressed the issue of injection site pain with regards to ESA treatment. All three RCTs found that subcutaneous epoetin-beta caused statistically significant less immediate pain sensation compared to subcutaneous darbepoetin-alpha.
Summary

The guideline recommends that supplements of vitamin C should not be prescribed as adjutants specifically for the treatment of anaemia of CKD. There is limited new evidence that indicates that vitamin supplementation may be beneficial in this patient population.

The use of androgens to treat anaemia in people CKD was not recommended in the guideline. Nandrolone decanoate is no longer used in clinical practice and concern over side effects had resulted in the treatment with this agent (as an adjunct to ESAs) being considered outdated despite some limited efficacy. The new evidence identified supported the current recommendations.

The guideline recommends that when prescribing ESA therapy patient preferences including pain on injection should be taken into account.

Clinical area 2: Assessment and optimisation of erythropoiesis

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Summary of evidence</th>
<th>Relevance to guideline</th>
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<tr>
<td>Related clinical questions from the guideline</td>
<td>Through an assessment of the abstracts from the high level RCT search 68 studies relevant to the clinical question were identified. The majority of studies identified focused on ESA therapy or iron supplementation. One limitation of research conducted within this field is that it does not clearly state the population in the abstract (i.e. non-dialysis, haemodialysis or peritoneal dialysis) and many earlier studies targeting haemoglobin levels for therapy are now not currently thought to be optimal (rapid update of the haemoglobin target thresholds in 2011) due to safety concerns on the level of haemoglobin in this population. The abstracts are summarised below:</td>
<td></td>
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<tr>
<td>Benefits of treatment with ESAs</td>
<td>New evidence was identified which may invalidate current guideline recommendations.</td>
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| Benefits of treatment with ESAs | New evidence was identified which may invalidate current guideline recommendations. |

In patients with ACKD what are the benefits and risks of correcting anaemia with ESAs compared to placebo or no treatment in reducing morbidity and mortality and improving quality of life? In patients with ACKD what are the benefits and risks of correcting anaemia with epoetin alfa compared to epoetin beta in reducing

**Benefits of treatment with ESAs**

Five studies, two systematic reviews and three RCTs, were identified. One systematic review and meta-analysis indicated that ESA treatment has a consistent and positive impact on exercise tolerance and physical functioning in ACKD adult dialysis patients. The second systematic review indicated that ESAs for CKD anaemia improve energy and physical

| New evidence was identified which may invalidate current guideline recommendations. |

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| morbidity and mortality and improving quality of life? In patients with chronic kidney disease what are the risks and benefits of early vs deferred correction of anaemia? In patients with ACKD, what factors determine the route of administration of ESAs? In patients with ACKD, what factors (including patient factors) determine the dose and frequency of ESA required to correct anaemia? | functioning in non dialysis patients.  

One placebo controlled RCT post hoc analysis reported that treating haemodialysis patients with epoetin alfa improved HRQOL. In addition one large RCT which assessed the effectiveness of darbepoetin alfa in comparison to placebo for patients with diabetes and ACKD not on dialysis was identified and analysed in two reports. The use of darbepoetin alfa conferred a small improvement in fatigue and overall quality of life but did not reduce the risk of either death or a cardiovascular event or death or a renal event but was associated with an increased risk of stroke.  

**Comparison of ESAs**  
Three ESAs (epoetin alfa, epoetin beta, darbepoetin alfa) were assessed and compared, where evidence permitted, in the original guideline. 14 studies relating to newer agents which have been licensed since the 2006 guideline was published have been identified. This includes;  

- **Methoxy polyethylene glycol-epoetin beta.** Six active comparator RCTS were identified assessing the long-acting erythropoietin |
What haemoglobin range should be maintained during anaemia treatment in CKD?

What is the most effective and safest dose, frequency, preparation and route of administration of iron in ACKD patients with functional iron deficiency prior to ESA treatment?

What is the most effective and safest dose, frequency, preparation and route of receptor activator methoxy polyethylene glycol-epoetin beta (C.E.R.A).

- Fortnightly subcutaneous C.E.R.A was found to be as effective as darbepoetin alfa in patients not on dialysis. For the same population of patients that had responded to fortnightly subcutaneous C.E.R.A. treatment every four weeks was also found to be effective and safe in maintaining stable haemoglobin levels. Once monthly C.E.R.A. treatment was found to be more effective maintaining stable haemoglobin levels than darbepoetin alfa every two weeks in haemodialysis patients.

- C.E.R.A has also been assessed in three Phase III studies against epoetin for correcting anaemia in CKD in dialysis patients either every two weeks or once a month.

- In addition a pooled analysis of all completed phase II and III for patients either on dialysis or not on dialysis indicated that
administration of iron in ACKD patients with functional iron deficiency receiving ESA treatment?

**Relevant section of guideline**
6.1, 6.3, 6.4, 6.7, 6.8, 6.9, 6.11, 6.12, 6.13

**Recommendations**
R24, R27, R30, R31, R32, R41, R42, R43

C.E.R.A. has a comparable safety profile to other ESAs.

- **Recombinant human erythropoietin (type not stated).** Two RCTs were identified that have assessed the efficacy of recombinant human erythropoietin (r-HuEPO) in comparison to darbepoetin alfa. Darbepoetin alfa was found to be non-inferior to r-HuEPO in a paediatric population and both agents maintained haemoglobin levels within the target range in peritoneal dialysis patients.

- **Epoetin zeta.** Epoetin zeta was found to have equivalent efficacy to epoetin alfa when administered either subcutaneously or intravenously. In addition, post hoc analysis of three studies indicates that epoetin zeta and epoetin alfa therapy are interchangeable with no clinical alteration with regards to efficacy, safety or dose in patients on dialysis.

- **Epoetin theta.** One RCT in haemodialysis patients indicated that
intravenous epoetin theta had a similar efficacy compared to 
epoetin beta in haemodialysis patients based on haemoglobin 
changes from baseline to end of treatment (non-inferiority). The 
safety profile was similar in both groups. 

- **HX575.** One RCT for HX575 (human recombinant epoetin alfa) the 
  first biosimilar ESA with marketing authorization in Europe 
  demonstrated therapeutic equivalence and a comparable safety 
  profile to epoetin-a, together with a comparable safety profile in 
  anaemia CKD patients on haemodialysis following.

Two RCTs that have directly compared agents addressed in the guideline 
were identified. One RCT was identified that compared intravenous 
epoetin alpha and subcutaneous epoetin beta. These agents showed an 
equivalent degree of efficacy in renal anaemia treatment of haemodialysis 
patients. The route of erythropoietin administration did not significantly 
affect the level of haemoglobin. A further RCT comparing epoetin alfa 
and darbepoetin alfa showed equivalent efficacy with regard to left 
ventricular parameters.
In addition studies relating to the following unlicensed agents have also been identified:

- **Epoetin omega.** One RCT found that subcutaneous epoetin omega provides greater bioavailability and anti-anaemic effect per administered dose than epoetin alpha in haemodialysis patients 31.

- **Epoetin delta.** Two RCTs have shown that epoetin delta has equivalent efficacy to epoetin alfa in dialysis patients with anaemia. This agent has since been withdrawn by the manufacturers 32,33.

**Early or late therapy**

One RCT assessed the efficacy of subcutaneous epoetin-alpha administered in early anaemia compared to in late anaemia in pre-dialysis CKD patients 34. The study was prematurely terminated due to contraindication of the subcutaneous administration route. However, the authors concluded that the early intervention to correct anaemia in CKD patients did not have a significant impact on left ventricular mass and time to dialysis/death was not significantly different between the treatment
groups. **ESAs: optimal route of administration**

Four RCTs were identified that have examined the route of ESA administration\(^{35,36,37,38}\). As the review process only considers abstracts it is not possible to determine if these studies met the inclusion criteria detailed in the guideline.

Three RCTs compared intravenous to subcutaneous administration of darbepoetin alfa. Two RCTs showed equivalent efficacy and no significant difference in required doses for either route of administration for maintenance of a stable haemoglobin level in haemodialysis patients\(^{35,36}\). Whereas, one RCT indicated that lower doses during intravenous treatment with darbepoetin alfa were needed in comparison to the subcutaneous route\(^{37}\). A further RCT assessed the effect of route of administration of erythropoietin on vascular access outcomes in haemodialysis patients\(^{38}\). The risk of vascular access failure was found to be greater with subcutaneous compared with intravenous administration of EPO two to three times weekly, however efficacy and dosage was not affected by route of administration.
ESAs: dose and frequency

One meta-analysis evaluated the potential dose savings when comparing epoetin alfa or beta to darbepoetin alfa when using an initial 200:1 conversion ratio, as indicated on the European label. The overall percentage dose savings attained when dialysis patients were converted from epoetin to darbepoetin alfa was 30 with greater dose savings noted with i.v. administration compared with subcutaneous. In addition, one RCT on haemodialysis patients evaluated erythropoietin doses on the basis of the computer recommendations or using standard anaemia management protocol. The Model predictive resulted in better anaemia management with fewer patients not maintaining target haemoglobin levels.

- **C.E.R.A.** Five RCTs assessing dose and/or frequency of the long lasting C.E.R.A. treatment were identified.
  - Three Phase II studies were identified, one concluded that 0.60 u/kg subcutaneous C.E.R.A. given twice monthly is a suitable starting dose for patients not on dialysis. Whereas two studies
A study indicated that subcutaneous C.E.R.A. or intravenous C.E.R.A. at up to once monthly intervals provides stable maintenance of Hb levels in dialysis patients.44,45.

- A Phase III study found that intravenous C.E.R.A. administered once every two weeks (Q2W) for Hb maintenance following direct conversion from darbepoetin alfa (DA) was safe and effective in dialysis patients.42 A further study reported that C.E.R.A. was effective in maintaining Haemoglobin concentrations in patients receiving dialysis treatment at weekly or Q2W.43.

- **Epoetin alfa.** Two RCTs in stage 3 and 4 CKD patients with CKD anaemia were identified.
  - One showed that administration of epoetin alfa at weekly and biweekly intervals are potential alternatives to twice weekly dosing.46 The second study showed that Q2W and Q4W dosing with epoetin alfa maintained haemoglobin levels and were non inferior to weekly dosing schedules.47.
  - Four RCTs in haemodialysis CKD patients were identified. One study demonstrates that once-weekly subcutaneous
administration of high dose epoetin alfa was as effective and safe as two or three times weekly administration in maintaining haemoglobin levels. A second dosing and scheduling study indicated that epoetin alfa can be initiated Q4W in anaemic CKD subjects. Likewise a third RCT found that the mean final haemoglobin levels of the Q2W and Q4W groups were statistically non-inferior to the weekly dosing. A post hoc analysis from this RCT demonstrated that patients with diabetes responded in a similar manner as patients without diabetes to extended dosing of epoetin alfa up to Q4W with and without diabetes as the primary cause of chronic kidney disease. One RCT did not show therapeutic equivalence of once-weekly intravenous epoetin alfa with conventional dosing regimens in haemodialysis patients.

- **Darbepoetin alfa.** One RCT found that administration of darbepoetin alfa biweekly could maintain haemoglobin level similarly to that obtained with weekly dosing in haemodialysis patients.
- **Epoetin beta.** One RCT showed that biweekly and once-weekly subcutaneous epoetin beta regimens were equivalent in the maintenance phase of anaemia treatment in long-term stable haemodialysis patients without diabetes.

### Optimal haemoglobin levels

Since the systematic review undertaken for the 2011 rapid update two studies were identified that related to the optimal haemoglobin levels. The first was a health economic cost-utility analysis to determine the cost-effectiveness of treating anaemic patients with chronic kidney disease (CKD) with ESAs to a low (9-10.9 g/dL), intermediate (11-12 g/dL), or high (> 12 g/dL) haemoglobin level target compared with a strategy of managing anaemia without ESAs. This analysis based on a publicly funded health care system indicated that using ESAs to target high haemoglobin levels has additional costs and worst clinical outcomes compared with using ESAs to target lower haemoglobin levels. The second study was a RCT which assessed the correction of anaemia in type 2 diabetes patients with CKD stages 3-4 to a target haemoglobin...
value in the ‘subnormal range’ (110-129g/l) or ‘normal range’ (130-149 g/l). Blood pressure, 24-h proteinuria and eGFR did not differ significantly during two year follow-up. There was no significant difference regarding Medical Outcomes Study 36-item Short-Form Health Survey score change or adverse event occurrence.

**Treating iron deficiency**

24 studies were retrieved that have investigated treating iron deficiency in CKD anaemia. From the abstracts the population studied was not always clearly defined in terms of dialysis status.

A systematic review and meta-analysis concluded that compared with oral iron, there was a significantly greater haemoglobin level in dialysis patients treated with i.v. (intravenous) iron however for patients with CKD, and the effect was small. Data for all-cause mortality were sparse, and there was no difference in adverse events between the i.v. and oral-treated patients.

- **Haemodialysis patients.** Eleven studies assessing iron supplementation in patients with anaemia and CKD on dialysis
(haemodialysis or peritoneal) were identified. The following active comparator trials were identified:

- In anaemic patients with CKD stage 5D on haemodialysis on ESA, rapid i.v. injection of ferumoxytol showed superior efficacy to oral iron at increasing haemoglobin levels with comparable tolerability.  
- Iron sucrose and Fe chloride were found to be safe and work equally well for haemodialysis patients in one RCT.
- One RCT found both iron saccharate complex and sodium ferric gluconate complex effective and safe for adequate repletion of iron stores.
- I.v. iron sucrose was more effective that oral iron at increasing haemoglobin levels and serum iron parameters. It was well tolerated and permitted reductions in the required dose of erythropoietin peritoneal dialysis.
- I.v. iron sucrose was found to be safe and more effective than oral iron gluconate at increasing serum iron serum ferritin, and transferrin saturation in paediatric replete patients on
| o | One RCT found investigating potential side effects of iron supplementation indicated that the incidence of side effects associated with i.v. iron-dextran was not different than that of i.v. iron-sucrose in end stage renal disease. |
| o | I.v. iron sucrose was well tolerated and more effective at increasing serum iron parameters and haemoglobin levels and allowed more reductions in the required dose of EPO in patients on haemodialysis than oral iron sucrose in one RCT. |
| o | One RCT indicated that oral iron (ferrous Fumarate) showed equivalent efficacy to i.v. iron at increasing haemoglobin, haematocrit and dry weight and reducing ESA dose requirement in anaemic patients using ultrapure dialysate. |

In addition the following three placebo controlled trials were identified:

| o | I.v. iron sucrose was shown to have a vasodilatory effect, but did not impair vascular reactivity in peritoneal dialysis (PD) patients in one RCT. |
| o | I.v. iron sucrose was an effective adjunct to ESA therapy in... |
anaemic patients with PD-dependent CKD and was administered safely at 300 mg over 1.5 h or 400 mg over 2.5 h in one RCT 67.

- Administration of intravenous ferric gluconate was superior to no iron therapy in anaemic dialysis patients receiving adequate ESA in one RCT 68.

- **Non-dialysis (ND-CKD).** Four studies in non-dialysis patient assessing iron supplementation in ND-CKD were identified:
  
  - One RCT compared i.v. sodium ferric gluconate complex with oral ferrous sulphate in anaemic, iron-deficient ND-CKD not receiving ESAs. 69 I.v. iron was more effective in increasing haemoglobin levels and caused greater improvements in quality of life, whereas oral iron achieved greater improvements in ferritin and TSAT.
  
  - One RCT found that i.v. ferric carboxymaltose was more effective and better tolerated than oral ferrous sulphate for treatment of iron deficiency in ND-CKD patients 70.
- I.V. iron sucrose administration was superior to oral ferrous sulphate therapy in the management of ND-CKD patients with anaemia in one RCT 71.
- One RCT indicated that bimonthly i.v. iron sucrose and oral iron sulphate had equivalent effects on haemoglobin levels and were equally safe. The supplementation elevated iron indices but did not increase haemoglobin synthesis in the study population of ESA-naïve, iron replete, non-dialysis patients with Hb >110 g/L CKD Stages 3-5 72.

- **CKD-not stated/mixed.** Five studies were identified in a population that was stated as mixed or CKD.
  - Ferumoxytol (newly licensed agent) was assessed in three studies; One placebo controlled RCT found ferumoxytol to be well tolerated in anaemic patients CKD stages 1 to 5 and 5D and have a similar safety profile to placebo 73. A report from the FDA summarised three clinical trials. Two evaluated patients with ND-CKD and a third trial assessed patients undergoing
haemodialysis. All three clinical trials showed that ferumoxytol administration increased the mean blood haemoglobin concentrations in comparison to oral iron \(^{74}\). A Phase III trial found that ferumoxytol was more effective than oral iron in increasing haemoglobin in patients who were not receiving ESA and in those who were receiving ESAs \(^{75}\).

- One RCT assessed side effects of i.v. iron dextran, i.v. sodium ferric gluconate complex and i.v. iron sucrose. Iron dextran had comparable adverse drug events to sodium ferric gluconate complex but more adverse drug events than iron sucrose and drug discontinuation occurred more often with iron dextran \(^{76}\).

- One study examined differences in proteinuria between i.v. iron sucrose and i.v. ferric gluconate after multiple doses. Although multiple doses of either i.v. iron did not increase basal levels of proteinuria, post-dose proteinuria was greater with iron sucrose than with ferric gluconate \(^{77}\).
Summary

CG114 makes many recommendations relating to ESA therapy and iron supplementation. The recommendations that relate to the new evidence identified above are summarised below along with a brief summation of the new evidence.

The guideline recommends that ESAs should be offered to people with ACKD who are likely to benefit in terms of quality of life and physical function. The majority of evidence supports this recommendation; however there is new evidence on a sub group of patients who may potentially be at increased risk of stroke due to ESA treatment.

The guideline recommends that the choice of ESA should be discussed with the patient on initiation of treatment and at subsequent reviews. The patient’s dialysis status, route of administration and availability should be considered. However at the time of the guidance there was no evidence to distinguish between ESAs in terms of efficacy. There is now new evidence relating to both new therapies and head to head comparisons of ESAs. However in terms of efficacy there is no evidence that would change
recommendations as the majority of studies report equivalent efficacy for these agents.

The GDG were unable to make any recommendations relating to the Early or deferred ESA therapy due to a lack of evidence in the original guideline development process. The new evidence is unlikely to change the current guideline.

The current recommendations state the prescriber and patient should agree the route of administration of ESA taking into account patient characteristics and preferences as well as drug costs. The frequency and dose of the ESA should determined by the duration and action and route of administration of the ESA. The guideline also states that for short-acting ESAs subcutaneous injection allows lower drug doses than intravenous injection.

There is new evidence on the scheduling and dosing of ESAs to maintain target haemoglobin levels. There are also new ESAs available which are longer lasting agents. In addition, there is new and conflicting evidence
around the differing efficacy of the route of administration for longer lasting ESAs (frequency doses \( \geq \) weekly). Furthermore, there is evidence that contradicts the current recommendation for short acting ESAs and indicates an increased risk of vascular access failure with this recommendation.

The guideline recommends that people with anaemia of CKD who are receiving ESAs should be given iron therapy, with patients with functional iron deficiency to be treated with i.v. iron. PD and ND-CKD who do not respond to oral iron will require i.v. iron. There are new agents and new evidence that assesses the relative efficacy and safety of iron supplementations that may alter guideline recommendations.

<table>
<thead>
<tr>
<th>Clinical area 3: Monitoring treatment of anaemia of CKD.</th>
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<tbody>
<tr>
<td><strong>Clinical question</strong></td>
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<tr>
<td>Related clinical questions from the</td>
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<tr>
<td>guideline</td>
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<td>----------------------</td>
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<tr>
<td>In patients with ACKD treated with ESAs, how frequently should iron status be checked?</td>
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<tr>
<td>How should ESA resistance be managed?</td>
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<tr>
<td>Relevant section of guideline</td>
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<tr>
<td>7.1, 7.2</td>
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<tr>
<td>Recommendations</td>
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<td>R46, R47</td>
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A post hoc analysis of a study which investigated the impact of European Best Practice Guideline prompting on patient outcomes was identified. The availability of a computerised clinical decision support did not affect anaemia management compared to centres that had a non-computerised clinical decision support. However, the study showed adherence to a European Best Practice Guideline improved attainment of anaemia indices.

The guideline makes recommendations related to the frequency of monitoring patients with ACKD. The study supported monitoring patients.

invalidates current guideline recommendations.
Table 2. Summary of articles from the focused search

<table>
<thead>
<tr>
<th>Clinical area 1: Benefits of treatment with ESAs</th>
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<tr>
<td><strong>Clinical question</strong></td>
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<tr>
<td>In patients with CKD and a malignancy what are the benefits and risks of correcting anaemia with ESAs?</td>
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**Relevant section of guideline**
6.1, 7.3

**Recommendations**
R24, R48

Whilst the guideline recommends that treatment with ESAs should be offered to people with anaemia of CKD who are likely to benefit in terms of...
quality of life and physical function patients with anaemia, CKD and malignancy are not specifically addressed within the guideline. With regards to resistance to ESAs the guideline provides a clinical definition that excludes other causes of anaemia such as intercurrent illness or chronic blood loss. Very limited evidence (one study) was found for the sub group of patients with ACKD and malignancy and ESA treatment, however there is some indication that this group of patients may have differing clinical outcomes relating to ESA therapy.
Numerous recent or ongoing clinical trials (publication dates unknown) were identified focusing on ESA therapy (C.E.R.A (33 placebo trials and 19 active comparators trials registered), 11 trials on epoetin alfa, 5 trials on epoetin beta, 2 trials on epoetin delta, 3 trials on hematide (peginesatide), two trials on HX575 and 24 trials on darbepoetin alfa (23 placebo trials and 1 active comparator trial)). There were also 25 trials registered that were investigating iron supplements (ferumoxytol, ferrous sulphate, ferric carboxymaltose and iron sucrose).

No evidence was identified that was relevant to research recommendations in the original guideline.

**Guideline Development Group and National Collaborating Centre perspective**

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Seven responses were received with respondents highlighting that there is no variation in the practice of the recommendations. However, two respondents reported substantial modifications in practice relating to the new haemoglobin targets which were noted to have had improved clinical practice and changes relating to the ESA therapy and iron management. In addition, one respondent highlighted that since publication of the guideline more literature has become available on treatment response, variability in haemoglobin levels, ESA therapy and iron management.

GDG members were also asked whether they were aware of evidence or practice which would demonstrate better value for money. A GDG member reported that the national contract for ESA therapy in Wales has allowed for cost savings for renal units only and one respondent stated that all ESAs had come off patent. However, whilst no audits of practice or implementation were
indicated as having been published since the guideline, the National Audit for Wales has been planned and the Renal Registry data for 2012 will be available in the New Year.

With regard for potential to improve important health outcomes the GDG feedback indicated that cycling haemoglobin levels are of a clinical concern and that there is still some uncertainty on the impact of leaving lower haemoglobin in resistant anaemia patients. In addition, two anecdotal efficacy or safety concerns about the recommended practice that may not be reported in the literature were reported by GDG members. These related to uncertainty around the toxic levels of iron and the target haemoglobin levels in the very elderly.

The potential for inequalities in access to services by patients who are pregnant or have intercurrent illness as well as age related inequalities were highlighted by two GDG members. The respondents were also asked if they were aware of any important or relevant areas not covered by the guideline; the classification and definition of kidney disease and ESA therapy for CKD patients with a malignancy were indicated. This feedback contributed towards the development of the clinical questions for the focused searches.

The majority of respondents felt that there is adequate evidence at this time to warrant an update of the current guideline.

**Implementation and post publication feedback**

In total 14 enquiries were received from post-publication feedback, most of which were routine.

Information was obtained from the NHS Information Centre for health and social care from a sample of anonymised GPs patient records data using the IMS Disease Analyzer. There were low numbers of patients diagnosed with CKD and anaemia who had been prescribed an ESA or an ESA plus an iron
supplement in each of the 5 study years, 2007-2011 (<1% in all years linked data and <2% not linked data). These numbers are very low and should be treated with caution as it may reflect poor recording by GPs.

No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

**Relationship to other NICE guidance**

The following NICE guidance is related to CG114:

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Review date</th>
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<tr>
<td>TA142 Anaemia (cancer-treatment induced) - erythropoietin (alpha and beta) and darbepoetin (2008)</td>
<td>Reviewed for update July 2011</td>
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<td>To be updated</td>
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**Related NICE guidance in progress**

<table>
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<tr>
<th>Guidance</th>
<th>Review date</th>
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<tr>
<td>Acute Kidney Injury</td>
<td>August 2013</td>
</tr>
<tr>
<td>TA Kidney disease (anaemia, chronic) – peginesatide</td>
<td>Due to delays in licensing timetable this will be subject to scoping in 2013</td>
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**Anti-discrimination and equalities considerations**

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of all adults and children who have a clinical diagnosis of anaemia.
associated with CKD. This includes people with non-dialysis CKD, people with established renal failure receiving renal replacement therapy, people with established renal failure receiving conservative management, and people after renal transplant surgery. The following groups were specifically outside of the scope as CKD is not the principal cause of the anaemia: haematological disease, acute and chronic inflammatory disease states, malignancy, acquired immunodeficiency syndrome and acute renal failure. The guideline covers the diagnostic assessment, management and monitoring of anaemia in primary, secondary and tertiary NHS care settings.

Conclusion

From the evidence and intelligence identified through the process, it suggests that some areas of the guideline may need updating at this stage, particularly in relation to:

- **Management of anaemia**
  - Nutritional supplements

- **Assessment and optimisation of erythropoiesis**
  - Benefits of treatment with erythropoiesis-stimulating agents (ESAs)
  - Comparison of ESAs
  - ESA route of administration
  - ESA dose and frequency
  - Treating Iron deficiency- correction and maintenance

- Wording and definitions relating to non-dialysis and classification of CKD stages are in line with CG73 CKD.

Review recommendation

The guideline should be considered for an update at this time.
Centre for Clinical Practice
14\textsuperscript{th} November 2011
Appendix I


