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Royal Cornwall Hospitals NHS Trust

Erythropoietin Use in Patients with Chronic Renal Disease (CKD) or Acute Renal Failure Clinical Guideline

V4.0

June 2022

1. Aim/Purpose of this Guideline

1.1. This guideline applies to medical, nursing and pharmacy staff involved in the care of adult patients treated with erythropoietic stimulating agent (ESA). This group includes dialysed and non-dialysed patients with anaemia caused by chronic kidney disease (CKD). **Any prescribing decisions falling outside this guideline MUST be approved by a consultant nephrologist.**

For the use of ESA in paediatric population, please refer to the *RCHT Paediatric team.*

1.2. This version supersedes any previous versions of this document.

Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation

The Trust has a duty under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 please see the Information Use Framework Policy or contact the Information Governance Team

Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1 Introduction

2.1.1 A major cause of **anaemia of CKD** is a reduction in erythropoietin production due to kidney damage. Other contributing factors include deficiency of iron, folate or vitamin B_{12}. Common symptoms include tiredness, shortness of breath, lethargy and palpitations. **Erythropoietin** is produced by the kidneys in response to low tissue oxygen levels and stimulates the bone marrow to form red blood cells. Its production decreases as renal disease progresses.

2.1.2 **Recombinant human erythropoietin** (an erythropoietic stimulating agent or ESA, formerly known as EPO) is a major advance in treating anaemia of CKD. By correcting the Hb levels it improves patient wellbeing and exercise tolerance, reduces the risk of cardiovascular disease and the need for blood transfusions. For more detail refer to the current version of the NICE guidance for managing anaemia in CKD (NICE, 2015 updated 2019). **Darbepoetin (Aranesp®)** is currently the ESA product of choice in RCHT.

2.2 Evaluation and diagnosis of anaemia of CKD

2.2.1 Investigating of anaemia is recommended in patients when:

- Hb level falls below 110g/L or
- symptoms of anaemia are present

2.2.2 An estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m2 in the community should trigger investigation into whether anaemia is due to CKD from the primary care provider. Other causes, like blood loss, iron, vitamin B12 or folic acid deficiency should be considered. When the eGFR is greater than or equal to 60 ml/min/1.73m2 the anaemia is more likely to be related to other causes.

2.2.3 **Baseline parameters**

For evaluation of anaemia and to obtain baseline parameters before ESA initiation it is recommended that the following tests should be performed:

- blood pressure
- full blood count
- iron status (including hypochromic red blood cells [%HRC] or reticulocyte Hb count [CHr] or, if this is not available, a combination of transferrin saturation [TSAT] and ferritin, as per separate iron deficiency guideline)
- serum ferritin (to assess iron stores)
- red cell folate and vitamin B_{12} levels within first 3 months
- C-reactive protein (to assess inflammation)
- renal function
- liver function

2.2.4 Erythropoietin levels should not be routinely monitored to diagnose or manage CKD anaemia.

2.2.5 In order to determine and manage iron deficiency follow the RCHT Clinical Guideline and the Clinical Protocol for intravenous iron available in the Documents Library.

2.3 ESA therapy initiation

2.3.1 Each patient diagnosed with anaemia of CKD should be referred to the Renal Anaemia service (ext. 3499).

2.3.2 Treatment with ESA will be offered to patients who are likely to benefit in terms of quality of life and physical function. The risks and benefits of treatment should be discussed with patients and their family, or carers if appropriate.

2.3.3 Before starting the treatment with ESA, the prescriber must be confident that the patient is medically stable, has well controlled blood pressure and is not iron deficient.

2.3.4 ESA must NOT be started in patients with poorly controlled hypertension.

2.3.5 All correctable causes of anaemia (including iron deficiency, inflammation and infection states) need to be addressed before commencing ESA. NB normal or high ferritin levels do NOT exclude iron deficiency. Ferritin is an acute phase reactant and may be elevated in infection or inflammation.

2.3.6 **Routes of administration**

ESA is given by:

- subcutaneous injection – preferred in patients NOT receiving haemodialysis (HD) to avoid unnecessary vein punctures.

- intravenous injection - preferred in HD patients in order to reduce the risk of developing neutralising antibodies and pure red cell aplasia.

2.3.7 ESA should be prescribed by brand name and patients should be maintained on a specific manufacturer's product. In an unusual situation of patients being admitted on a brand unavailable in RCHT, consult with a specialist nephrologist and contact Medicines Information (ext. 2587) for advice regarding dose conversion.

2.3.8 ESA should not be used as a substitute for red blood cell transfusions in patients requiring immediate correction of anaemia.

2.3.9 **Initial dose**

Calculate the initial dose of ESA based on patient's actual body weight. Clinical circumstances should be taken into consideration when determining the initial dose. For Darbepoetin (Aranesp®) prescribe **0.45microgram/kg WEEKLY** (for s/c and i/v):

weight	suggested **weekly** Aranesp® dose
<55kg	20mcg
55-79	30mcg

weight	suggested **weekly** Aranesp® dose
80-104	40mcg
105-124	50mcg
125-150	60mcg
>150	70mcg

2.3.10 At the time of writing this guideline a pre-filled syringe was the device of choice for the administration of Aranesp® due to pricing and availability reasons. However, the choice of device should also be based on patient's preference and ability to administer. If in doubt refer to the Renal Anaemia service or Renal Specialist Pharmacist. Aranesp® is available as a pre-filled syringe and pre-filled pen, both in a wide range of doses.

2.4 ESA correction and maintenance dosing

2.4.1 The dose adjustments should be based on patient's Hb level, rate of change in Hb concentration, current ESA dose and clinical circumstances.

2.4.2 Each ESA dose change should be clinically checked by a renal pharmacist, recorded on the recognised renal database system and communicated to the patient in an appropriate manner.

2.4.3 **Hb range**

The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD due to the increased risk for death, serious adverse cardiovascular reactions, and stroke. The **aspirational Hb range** should be maintained **between 105 and 115g/L**.

2.4.4 ESA should NOT be administered to patients with Hb>120g/L.

2.4.5 To keep the Hb within the aspirational range, do not wait until Hb levels are outside the range before adjusting treatment (for example, observe the trends and take action when Hb levels are within 5 g/litre of the range's limits: <105 or >115g/L; if Hb raises above 110g/L the dose can be reduced and subsequently adjusted depending on Hb levels).

2.5 Correction phase

2.5.1 Dose increase

In inadequate response dose adjustment should be prescribed according to the product licence. The dose of Darbepoetin (Aranesp®) can be increased by approximately 25% if increase in Hb is less that 10g/L over 4 weeks from the first administration.

2.5.2 Dose decrease

Rise in Hb greater than 20g/L over a 4 week period should be avoided. If it occurs it is recommended to decrease the dose rather than interrupt the treatment. The dose should be reduced by approximately 25%, and Hb monitored at least monthly.

2.5.3 If Hb continues to rise, the dose should be temporarily withheld until Hb begins to decrease, at which point Aranesp can be restarted at the dose approximately 25% lower than the previous dose. If the haemoglobin rises by greater than 30g/L in one month the Anaemia CNS/ nurse employed in renal services must discuss dose adjustments with the patient's nephrologist.

2.5.4 **Dose changes in the correction phase should not be made more often than monthly**. If Hb levels change rapidly consult a specialist nephrologist.

2.5.5 Monitoring frequency

Hb level should be monitored at least monthly until it is stable and the correction phase complete.

The marker of iron status (see paragraph 2.3 and 2.5) should be monitored every 3 months.

2.6 Maintenance phase

2.6.1 Injection frequency

The frequency of injections can be decreased in patients maintaining Hb targets for at least 6 months. When increasing the dose interval calculate the dose of Aranesp® following the pattern below:

Current dose:	Equivalent to:
10mcg weekly	20mcg fortnightly
20mcg weekly	40mcg fortnightly

See the Summary of Product Characteristics for more detail (eMC, 2018)

2.6.2 **Dose and schedule adjustment**

2.6.2.1 If the target Hb levels are not maintained, adjust the dose of Aranesp® by either changing the dose or the interval between the doses. Base this decision on factors like patient's ability to follow changed injections frequency and remaining stock already delivered to the patient.

2.6.2.2 Any adjustments to the dose or schedule of injections should not be greater than approximately 25% of the initial dose.

2.6.2.3 Maintenance dose changes should not be made more frequently than monthly.

2.6.3 **Monitoring frequency**

2.6.3.1 In patients whose Hb levels have been maintained within the target for the last 6 months, the monitoring interval can be increased up to 3-monthly. In any case of Hb levels falling outside the target range more frequent monitoring is advised.

2.6.3.2 When changing the route of administration it is recommended to maintain the dose and frequency of injections and monitor Hb levels at least monthly until stable.

2.6.3.3 Iron, folic acid and vitamin B12 status should be evaluated at least 3 monthly and appropriate supplementation offered to deplete patients receiving ESA maintenance therapy (see paragraph 2.3 and 2.5).

2.6.3.4 Additionally, serum ferritin level should be checked 3 monthly to prevent the iron overload. The level of 800mcg/L should not be exceeded, and in order to prevent this from happening the dose of iron should be reviewed when ferritin levels reach 500mcg/L.

2.6.3.5 Blood pressure should be regularly monitored and documented.

2.7 Cautions and contraindications

2.7.1 Poorly controlled hypertension (see paragraph 3.3.1.). A significant rise in blood pressure while on the ESA treatment should be promptly reported to medical staff and recorded in the handover notes on the recognised renal data system. EPO can be given when hypertension is present THOUGH medical staff must be informed of the patient's blood pressure as soon as possible after the EPO is given.

2.7.2 Resistance to ESA therapy

2.7.2.1 In patients with poor Hb response to Aranesp® despite repeated dose escalations or reaching the dose of 100microgram/week (or 1.5microgram/kg/week in patients with low body weight), alternative explanations to lack of response should be considered.

2.7.2.2 Some CKD patients with anaemia who are offered an ESA are 'ESA resistant' – that is, their condition consistently fails to respond to the ESA treatment. These patients often receive large doses of ESA, sometimes with blood transfusion, with limited benefits and at significant cost to the NHS. Many CKD patients with anaemia receiving an ESA are admitted with an intercurrent illness – such as pneumonia – which may temporarily render them acutely hyporesponsive to that ESA. (NICE, 2015).

2.7.3 Malignant disease

2.7.3.1 ESAs are growth factors which stimulate erythrocytes production. Erythropoietin receptors may be expressed on the surface of some tumour cells which raises concerns that ESA could stimulate the growth of tumours. The decision to administer ESA should be taken with patient's participation and based on a benefit-risk assessment

2.7.3.2 ESA should NOT be routinely prescribed for patients with active malignant disease. It can be used with caution in patients with solid or lymphoproliferative malignancies. If a CKD patient has a haemotological maliginancy such as chronic lymphocytic leukaemia; EPO should not have any adverse promoting effect on lymphoid lineage cells and therefore there is no contraindication to its use.

2.7.4 ESA induced pure red cell aplasia (PRCA)

2.7.4.1 Routine screening for anti-erythropoietin antibodies is not recommended

2.7.4.2 Consider the ESA induced PRCA in patients on long term ESA therapy (over 8 weeks) who develop:

- A sudden otherwise unexplained decrease in Hb concentration at the rate of 5-10g/L per week or requirement of transfusions 1-2 times a week
- Platelet and white cell count within the norm
- Absolute reticulocyte count <10,000/microliter
- Serum ferritin increases to very high levels, as does the transferrin saturation. Thus, serum ferritin levels of >1000 µg/L and transferrin saturation levels of >70% are characteristic of PRCA.

2.7.4.3 If diagnosis of ESA induced PRCA is confirmed the ESA treatment should be discontinued.

2.7.5 Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in ESA patients. When ESA treatment is started patients should be educated about signs and symptoms and to monitor for skin reactions. ESA treatment should be stopped immediately if SCARs symptoms occur.

2.7.6 ESA should be used with caution in patients undergoing CABG or orthopaedic procedures, suffering from epilepsy, Hepatitis C, acute and chronic liver disease, sickle cell anaemia, hyperkalaemia, thrombocytosis, and latex allergy. For the full list of cautions, complications and side effects check Aranesp®'s SPC (eMC, 2018).

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Investigation of anaemia before prescribing treatment
Lead	Anaemia Management Nurse employed within Renal Services, RCHT
Tool	The erythropoietin dose, frequency and haemoglobin level will be monitored by the Anaemia Management Nurse each month. This data will be shown on excel documents stored on Oesdata13_server\Data13. This is a shared drive accessible by staff employed within renal services.
Frequency	The Anaemia Management Nurse will present this data annually at renal audit meeting.
Reporting arrangements	Any erythropoietin prescribing undertaken by the Anaemia Nurse Manager will be subject to clinical supervision by all four consultant nephrologists annually. If discrepancies are identified at these reviews they will be reported to the medical divisional lead for governance and safety, RCHT and the Anaemia Nurse Manager will be subject to further training and education.
Acting on recommendations and Lead(s)	The Anaemia Management Nurse will act on recommendations within 1 month of the annual prescribing review.
Change in practice and lessons to be shared	If discrepancies are identified following clinical supervision of prescribing undertaken by the Anaemia Nurse Manager the clinical supervision sessions will take place more frequently; every 3 months. Lessons learned will be shared with all the relevant stakeholders.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Inclusion & Human Rights Policy' or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Erythropoietin Use in Patients with Chronic Renal Disease (CKD) or Acute Renal Failure Clinical Guideline V4.0
This document replaces (exact title of previous version):	Erythropoietin Use in Patients with Chronic Renal Disease (CKD) or Acute Renal Failure Clinical Guideline V3.0
Date Issued/Approved:	17 June 2022
Date Valid From:	June 2022
Date Valid To:	June 2025
Directorate / Department responsible (author/owner):	Sharon Benton, Anaemia CNS
Contact details:	01872 253499
Brief summary of contents:	The policy details the process for the use of Erythropoietin in renal patients. The policy includes guidance to support effective and safe prescribing of the drug.
Suggested Keywords:	Anaemia Kidney Renal Haemoglobin Erythropoietin Haemotynics EPO ESA
Target Audience:	RCHT: Yes CFT: No KCCG: No
Executive Director responsible for Policy:	Medical Director
Approval route for consultation and ratification:	Renal Governance Meeting
General Manager confirming approval processes:	Racheal Pearce

Information Category	Detailed Information
Name of Governance Lead confirming approval by specialty and care group management meetings:	Siobhan Hunter
Links to key external standards:	Nice Clinical Guideline 39: Anaemia Management in People with Chronic Kidney Disease. NICE, London http://guidance.nice.org.uk/CG114
Related Documents:	RCHT Patient Identification Policy RCHT Consent to Treatment/Examination RCHT Standards of Record keeping RCHT Infection Control NMC Code of Conduct, Performance and Ethics Prescription or Patient Group Direction for appropriate medications as detailed within this protocol NICE (2015, updated 2019) – chronic kidney disease: managing anaemia. nice.org.uk/guidance/ng8 UK Renal Association (2007) Clinical Practice Guidelines; Module One Chronic Kidney Disease, (2nd Edition) UK Renal Association, Hampshire.
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet & Intranet
Document Library Folder/Sub Folder:	Clinical / Renal

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
Date Unknown	V1.0	Initial issue	Sharon Benton, Anaemia CNS
09/12/2015	V2.0	New Trust template. Blood result parameters updated in line with Pathology Harmonisation Guidance 2007.	Sharon Benton, Anaemia CNS
March 2019	V3.0	Full review. Removal of flowchart. Change from EPO to ESA. Re-formatting throughout.	Aleksandra Rutkowska, Pharmacist, RCH
June 2022	V4.0	No Changes. Updated to latest accessible Trust template	Sharon Benton Anaemia Cancer Nurse Specialist

All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.
This document is only valid on the day of printing

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust Policy for the Development and Management of Knowledge, Procedural and Web Documents (The Policy on Policies). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity & Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Erythropoietin Use in Patients with Chronic Renal Disease (CKD) or Acute Renal Failure Clinical Guideline V4.0
Directorate and service area:	Specialist Medicine, Renal
Is this a new or existing Policy?	Existing
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Sharon Benton, Anaemia Cancer Nurse Specialist
Contact details:	01872 253499

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	The aim of the policy is to maintain the haemoglobin level between 100 and 120g/l in the majority of patients.
2. Policy Objectives	To ensure the patient is correctly assessed before Erythropoietin is prescribed.
3. Policy Intended Outcomes	To achieve the above safely.
4. How will you measure each outcome?	As per section 3 of this guideline, 'Monitoring and Compliance Effectiveness'.
5. Who is intended to benefit from the policy?	Patients with chronic kidney disease or failure referred for initiation of Erythropoietin treatment. All staff administering Erythropoietin therapy.

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/ visitors: No • Local groups/ system partners: No • External organisations: No • Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	Renal Governance Group
6c. What was the outcome of the consultation?	Approved
6d. Have you used any of the following to assist your assessment?	Chronic Kidney Disease: Managing Anaemia NICE guideline (NG8) Published June 2015

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	

Protected Characteristic	(Yes or No)	Rationale
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment:
Sharon Benton, Anaemia Cancer Nurse Specialist

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis