Management of Adults with Sickle Cell Disorder

These Guidelines were created by The Red Cell Network Haemoglobinopathy Coordinating Centre.

They exist to standardise care for adults with Sickle Cell Disorder within the North Central London and East Anglia regions.

Trusts choosing to adopt these standards must complete the template in Appendix 2.

A web version of this document is available on The Red Cell Network website.

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Contents

Sickle Cell Disorders (SCD) Guideline

Introduction

Sickle Cell is the commonest inherited single gene disorder in the UK with an estimated 15000 people living with Sickle Cell Disorders (SCD) and approximately 300 babies born annually. The majority (80%) live in or around London. SCD predominantly affects people from African and Caribbean backgrounds, however the genes are inherited **independent** of ethnic origin. The conditions are inherited in an autosomal recessive pattern. When inherited from both parents a mutation affects the oxygen carrying pigment, haemoglobin, in the red blood cells. On exposure to low oxygen conditions, the haemoglobin distorts and the red cells become stiff, sticky and misshapen ("sickled"). The “sickled” cells cannot squeeze through the smaller blood vessels and stack up causing blockage (vaso-occlusion), severe pain (“painful crisis”) resulting in damage to tissues and organs. In addition, the red cells are fragile with a high rate of red cell destruction (haemolysis) causing inflammation, endothelial dysfunction and anaemia, all of which are risk factors linked to stroke, thrombo-embolism, ulcers and chronic kidney disease. Infection (fever), exposure to cold, dehydration, strenuous exercise, menstruation, pregnancy and emotional stress can all trigger a vaso-occlusive painful crisis. Patients with SCD can suffer with a variety of acute and chronic problems. Acute complications include profound anaemia leading to aplastic crisis, sequestration of spleen and liver, life threatening infections, stroke, acute chest syndrome. Chronic complications include avascular necrosis of the joints, pulmonary hypertension, kidney disease and / or retinopathy. Pregnancy, routine surgery and some dental care require specialist input to reduce the risk of acute, life-threatening, complications.

Healthcare in these patients is complex and it is essential that timely input is sought from specialist red cell teams in order that care is delivered appropriately in line with best practice.

Patients may have had previous traumatic experiences during painful episodes; treating patients with kindness, compassion and as an expert in their condition is essential. Unhelpful attitudes from healthcare workers can delay a patient’s recovery and has long term consequences.

The All-Party Parliamentary Group for Sickle Cell and Thalassaemia published ‘No One’s Listening’ in 2021. The report showed, despite changes to the services and national guidance, that there were still many patients with SCD who were not receiving the expected standard of care, were not being listened to and who had, sadly, died following failures in their care (McFadden, 2021).

The four key NHS principles of **respect, dignity, compassion** and **care** are core to how patients are treated. Care should be coordinated under NHS ‘Act Now’ principles; Analgesia, Compassion, Test / Trigger, Notify, Oxygen, Watch (NHS, Act Now*)* ensuring compassionate leadership and a culture of high- quality care.

SCD are multisystem conditions. Care of adult patients involves surveillance to detect the emergence of chronic complications and implementation of appropriate management. Every patient must have a comprehensive annual review by a red cell specialist.

Service provision in England

NHS England commission specialist haemoglobinopathy services with a dedicated Clinical Reference Group (CRG) for the care of patients with

SCD and other inherited red cell disorders. Patient care is coordinated via a National Haemoglobinopathy Panel (NHP), ten Haemoglobinopathy Coordinating Centres (HCC) over 25 Specialist Haemoglobinopathy Teams (SHT) and several Local Haemoglobinopathy Teams (LHT). This system was introduced with the aim of reducing morbidity / mortality, to ensure equality of access and to improve the experience of the patients. All patients with SCD should be allocated to a specific SHT who are responsible for ensuring 24/7 specialist advice and appropriate ongoing care with, at a minimum, a specialist review annually. For complex care advice and support can be obtained from the HCC and NHP. Services are reviewed by the Haemoglobinopathy Peer Review process against document quality standards (UKFHD, 2021). All patients with SCD have an electronic summary (specialist patient care plan) outlining important aspects of their care and pain

management regime, it is essential that this electronic record is accessed should the patient require acute care. There is a national data base of patients with inherited red cell disorders, which includes all SCD, the national haemoglobinopathy register (NHR), which should contain basic patient information (NHS number), linked via their allocated SHT with detailed information from the annual review and any notifiable adverse events. The introduction of the NHR has transformed the ability for red cell data management teams to provide key dashboard, audit and research data (NHR).

Summary

Sickle cell disease is a complex, multi-system condition requiring specialist knowledge and a multi-disciplinary approach. This guidance applies to **all staff**, medical, nursing and allied health professionals who are involved with the care of these patients. Key principles are to:

- Treat promptly.
- Monitor correctly.
- **Treat pain as a medical emergency**: be aware and sensitive.
- Be alert to critical warning signs. **Patients can often be sicker than they first appear and can deteriorate quickly and unexpectedly.**
- Manage early and aggressively.
- Engage and listen to the patient; respect patient preference, ensure physical comfort and emotional support.

Senior specialist input must be sought in the case of acutely ill patients; this guidance does **not** replace urgent discussion and input from the red cell consultant grade staff. The guidance has been alphabetically ordered by organ systems (Abdominal; Circulation; Endocrine; Infection; Mental Health; Neurology; Ophthalmology; Orthopaedic; Pain; Renal; Sexual Health; Transplantation and novel treatments) covering both acute and chronic aspects of care. This guidance works in conjunction with local specific guidelines outlining detailed aspects of treatment for example, antibiotic use, pre surgical assessment, the blood transfusion policy.

Aim

The aim of this guideline is to provide staff with an overview of the safe, effective and timely clinical care for adult patients with clinically significant sickle cell disorders (SCD), for example HbSS, HbSC, $HbSb^0$.

Inheritance

Detail on phenotypes, genotypes and inheritance are not included within this guidance. For further information refer to *https://www.sicklecellsociety.org/resource/inheritance-sickle-cell-anaemia*. This guidance covers clinically significant homozygous genotypes, such as HbSS, HbSC, $HbS\beta^0$. Generally individuals who inherit HbS alongside a normal haemoglobin, ie HbSA, 'sickle cell trait' do not present with significant sequelae, are not covered in this document however further advice can be sought from senior members of the red cell team.

References

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Abbreviations and terminology

- AXR Abdominal X Ray
- ACE inhibitor Angiotensin converting enzyme inhibitor
- ACS Acute Chest Syndrome
- ED Accident and Emergency or Emergency Care Department
- ARCE Automated Red Cell Exchange
- AVN Avascular necrosis
- CBT Cognitive Behavioural Therapy
- CT Computerized Tomography scan
- CXR Chest X Ray
- ECHO Echocardiography
- HCC Haemoglobinopathy Coordinating Centre
- Hb Haemoglobin
- ICU / HDU Intensive Care or High Dependency Unit
- IQ Intelligence quotient
- LHT Local Haemoglobinopathy Team
- LMWH Low Molecular Weight Heparin

MC&S Microscopy, culture and sensitivity

MDT Multidisciplinary Team

- MRA Magnetic resonance angiogram (blood vessels and blood flow)
- MRCP Magnetic resonance cholangiopancreatography

- MRI Magnetic resonance imaging

- 6MWT 6 minute walk test
- NHP National Haemoglobinopathy Panel
- NSAIDS Non-steroidal anti-inflammatory drugs
- NT-proBNP N terminal pro b type natriuretic peptide
- PCA Patient Controlled Analgesia
- SCD Sickle Cell Disorders
- SHT Specialist Haemoglobinopathy Team
- sPCP Specialist patient care plan (**example** Appendix 10)
- TCD Transcranial doppler
- TRV Tricuspid regurgitant jet velocity
- uPCR Urine protein creatinine ratio
- USS Ultrasonography
- VOC Vaso-occlusive crisis

Process for monitoring compliance and effectiveness

Adherence to this guideline will be the responsibility of the HCC. Red cell services are reviewed by the Haemoglobinopathy peer review process against documented quality standards (UKFHD, 2021). The HCC and local data management teams will coordinate regular review, collection of dashboard data and audit of compliance. Details of data collected, annual audits, MDT meetings and incidents, errors and concerns can be obtained from the HCC data management team (see Appendix 2 on who and how to contact).

Dissemination and implementation

This guideline replaces all previous guidance for the care and treatment of adult patients with SCD. The guidance will be made available via local trusts / hospitals intranet. Managers of local trusts must ensure that all staff working with patients living with SCD are aware of and have access to the same standard document.

Expectations / Duties within the organisation

- **Responsible Officer:** The HCC lead has authored and authorised this guideline however ownership of the guidance sits with local Medical Directors who have executive ownership.
- **Local Service and Clinical Managers** are responsible for ensuring staff are aware of and have access to this policy and receive training and updates. All staff who may have contact with, or be involved in, the care of patients with SCD should be signposted to the guideline. Staff should be reminded of the guidance at least two yearly via screen savers and / or communication cascades.
- **Specific responsibilities:**
  - It is the responsibility of the **clinical area** nursing and medical team to monitor all patients with sickle cell in line with this guidance; to ensure appropriate handover and ensure test results are obtained, reviewed and acted on in a timely manner.
    - In-patients with SCD should be reviewed daily by the local Haematology **Red Cell team**.
  - Where patients are not admitted under the local haematology red cell team, it is the responsibility of **the admitting team** to inform the red cell team of the patient's attendance at the point when they are referred to them.

Equality Impact Statement

An Equality Impact Assessment (EIA) of this guidance was undertaken in November 2023 which concluded that there was no negative impact on any of the protected equalities groups (**Appendix 1**). It was noted that there are some differences in the treatment via blood transfusion depending on sex, age and pregnancy but these differences are based on national good practice guidance.

Contact Details

Please refer to **Appendix 2** for details of how to contact the red cell team in and outside of normal working hours and **Appendix 4** for details on other clinical teams that patients should be referred to for specific complications. (*Appendix 2 and Appendix 4 must be completed locally LHTs should include how to make contact with SHT / HCC teams to discuss care and transfer if necessary with any local arrangements for referral to other clinical teams (for example obstetric / surgical / urology) included in one or both documents)*.

GENERAL ASPECTS OF CARE

Acute presentation

Rapid assessment, prompt treatment and effective monitoring are essential in achieving a successful outcome (summary provided **Appendix 3**). The patient may present via accident and emergency or may deteriorate during in-patient or day case care.

Initial Assessment

The purpose is to establish how unwell the patient is by identifying any current or pre-existing factors that might increase the chance of complications. The aim is to treat promptly in line with best practice. Each attendance should be treated as a new episode of illness worthy of full evaluation and management. **Ensure that pain relief is administered promptly**; this will enable better assessment of the patient. The national standard is for patients must be given **the first effective dose** of analgesia within **30 minutes** of arrival aiming for the pain to be **under control within two hours**. Consider and record:

The presenting complaint

- History of presenting complaint as outlined by patient or carer.
- Site and severity of any pain.
- How typical the pain is, or isn't, compared to usual painful episodes ('crises').
- What recent analgesia has been used.
- Any precipitating event, for example any diarrhoea, vomiting, upper respiratory tract infection, stress etc.
- Type of sickle cell disorder (HbSS, HbSC, HbSβ^0 etc).

Past Medical History

- Hospital that the patient usually attends for care.
- Obtain specialist patient care plan (sPCP) and record:
- Sickle phenotype / genotype, baseline haemoglobin, steady state O2 saturations and baseline creatinine.
- Previous complications (ACS, Stroke, priapism, osteomyelitis, cholecystitis, gallstones, venous thromboembolism).
- Recommended pain protocol.
- Any treatment regimens or noted problems for example, whether patient is on hydroxycarbamide, a transfusion program, has iron overload or problems with venous access.

- Transfusion history; any prior transfusions (or advanced directives declining transfusion), any known atypical red cell alloantibodies, any previous transfusion complications.

Examination

Patient examination should include:

- Examination for soft tissue swelling over site of pain.
- Respiratory examination
- Abdominal examination looking for hepatosplenomegaly

Initial Investigations

Refer to local guidance on sampling, labelling, how to send to the laboratory and how to access the results in a timely manner depending on the patient's clinical need. Routine bloods should include:

- Full blood count and Reticulocyte count
- Renal profile
- Liver profile
- LDH
- Group and antibody screen if patient NOT previously known

to hospital. Discretionary bloods, if clinically indicated, may include:

- Bone profile (for example dehydrated)
- CRP (if presentation suggestive of infection0
- Haemoglobinopathy screen ***IF*** the diagnosis is unknown, on a regular transfusion program or advised by haematology team. Please discuss with red cell team before sending.
- Clotting profile (important if likely intervention, e.g. line planned)
- Blood transfusion specimen(s) only if transfusion likely (infrequent attenders or acutely ill patients.
- Pregnancy test in females of reproductive age.

Note: Blood transfusion requests must be clearly **labelled as sickle cell patient**. Inform Blood Transfusion Laboratory if the patient is not known to the hospital so they can contact other hospital to get essential details on antibodies, red cell phenotype and last transfusion). 'New' patients or patients known to have red cell antibodies will require additional samples for referral to reference laboratory. Failure to do so leads to considerable delays in treatment and can be life-threatening.

Critical warning signs

The following indicate unpredictable complications. The Red Cell team Consultant Haematologist, must be contacted **urgently** regarding any patient who:

- Is Hypoxic (saturations measured on air <94% or > 4% drop from baseline); Pa O2 <8.5pa; new chest signs on examination with or without chest pain.
- Is deteriorating or has a previous episode of deterioration when unwell.
- Reports to be feeling very unwell, atypical to previous episodes.
- Shows signs of sepsis or fever with a temperature of > 38ºC or positive cultures.
- Is haemodynamically unstable.
- Shows neurological signs: altered GCS, meningism, focal neurology, a new asymmetrical weakness, severe headache.
- Shows signs of symptomatic anaemia or Hb < 20 g/L from baseline.
- Shows abdominal complications: abdominal distension, absent bowel sounds, rebound and guarding usually absent, dilated loops on AXR, large liver or spleen.
- Reports to have, or is showing signs of, uncontrolled pain.
- AKI which needs to be interpreted in the context of their baseline Cr - patients with sickle cell cannot concentrate their urine normally so often run a low creatinine level; an increase from baseline may suggest acute renal failure (baseline creatinine recorded in the sPCP). Urgent referral to renal team with red cell team informed.
- Has a respiratory rate that falls to <12/min when all opioids should be stopped and doctors informed urgently.
- New cytopenias (thrombocytopenia, neutropenia)
- Evidence of multi-organ failure, particularly in the context of new cytopenias and neurological symptoms which may indicate acute fat embolism syndrome.

Management

- Analgesia: patients must be given **the first effective dose** of analgesia within **30 minutes** of arrival aiming for the pain to be **under control within two hours**
- Prescribe and encourage oral anti-emetics (note: cyclizine must not be given intravenously).
- Sickle cell patients are functionally hyposplenic and are usually on long-term prophylactic antibiotics. If unwell a low threshold to commence empiric antibiotic treatment based on local microbiology guidelines is appropriate.
- Laxatives should be prescribed and bowel movements noted for patients on opioids.
- VTE prophylaxis: patients with sickle cell disease are at medium risk of VTE, ensure the trust guidelines are followed. Should the patient have had a previous VTE ensure time prescribing and administration of medication unless contraindicated.
- **Fluid Replacement.** The treatment most likely to influence the resolution of a crisis is hydration. Patients become dehydrated because they cannot concentrate urine and increased blood viscosity exacerbates sickling.
- Try oral route, however, intravenous fluids maybe required.
- Gentle fluid resuscitation is preferred as some patients have compromised cardiac reserve or abnormal renal function.
- Do not exceed 4 litres in 24hrs intravenously unless severely dehydrated. Total of 70-90 mL/kg body weight per 24 hours. Prescribe a crystalloid solution with potassium replacement if indicated (corresponding to 70mLs/kg/day).
- Check U&E for hypokalaemia and change of creatinine from baseline.
- **Venous access.** Can be challenging, even blood tests can be difficult and it is essential to engage and discuss options with the patient and to use their expert knowledge of how access is usually obtained. SCD patients are at risk of thrombosis, for which central lines are a risk factor. However, access should not be delayed where clinically necessary. If inserted remove asap and no later than 48 hours after insertion. The reader should refer to **Appendix 2** which shows local contact details of how obtaining access can be escalated.
- **Oxygen:** While there is no proven benefit in non-hypoxic patients, many report symptomatic benefit and oxygen should be prescribed at the patient's request even if their O2 saturation is normal.
    - Monitor pulse oximetry OFF oxygen.
- Saturations <94% or a reduction of >4% from baseline is a critical warning sign. Escalate and follow the management for acute chest syndrome.
    - Do not assume chronic hypoxia unless clearly documented in the sPCP (example **Appendix 10**).

Monitoring

It is essential to ensure regular and rigorous monitoring to ensure any 'critical warning signs' are detected and acted on appropriately. Patients may be reasonably well on admission and then deteriorate suddenly and very rapidly.

- **Observations:** At a minimum observation, heart rate, respirations, blood pressure, oxygen saturation (on air), temperature and GCS must be performed every 30 minutes from onset of pain until pain relieved then four hourly. If on strong opiates, this should be done hourly for at least the first six hours. If patient is on PCA continued observations should be in line with local policy.
- Height and weight on admission
- Input chart throughout stay, output recordings if indicated / requested.
- Excess opioid analgesia can cause respiratory depression. If respiratory rate falls below 12 per minute or saturations decrease significantly patients should be assessed immediately. Naloxone should be avoided if possible as this can cause recurrence of severe pain that may be difficult to control. Opioids must be stopped and patients watched closely with senior medical input.

Nursing Care

- Observations: aim early detection and prevention of acute medical sickle cell complications in the hospital setting.
- Pain management: aim rapid and effective pain relief, the prevention of known complications and side effects.

- Hydration and diet: aim to prevent dehydration and to provide adequate nutrition.
- Toilet / Hygiene / Environment: aim to meet the patient's needs and maintain good hygiene.
- Complications of sickle cell disease: Aim to be aware of specific complications of sickle cell disease and alert medical staff appropriately (see '**critical warning signs'**).
- Ensure physical comfort and emotional support; patients should be nursed in a warm environment and kept away from draughts or open windows.
- Incentive spirometry should be performed and recorded in accordance with local policy or as directed by the local red cell team.
- Nursing in isolation should be considered in line with trust guidelines.

Admission

- Initial triage, assessment and management will be performed by ED or Ambulatory Care staff where the hospital has this service see **Appendix 2** for details.
- Patients with uncomplicated sickle cell crisis will be under the care of the medical team until formally transferred to the haematology team.
- All patients with complicated crises should be admitted.
- For patients with high-risk disease or who are very ill, the haematology team, or medical team with haematology input, will review the patient in ED.
- Admission may require coordination of two teams when the presenting complaint is not directly related to the SCD.

Discharge

Even if the reason for admission is not sickle related the red cell team should be involved and confirm that the patient is fit for discharge. Patients attending ED or ambulatory units must remain for two hours for observation prior to discharge. Admitted patients should be supplied with appropriate TTAs, including oral analgesia, a timely red cell outpatient appointment, reminded how to obtain specialist support (usually via the red cell nursing team see **Appendix 2**) and advised of any potential side effects of the treatment received. Some trusts may have access to community based follow up and if so the sickle cell nursing team should be notified see **Appendix 2**. A copy of the discharge summary should be made available to all relevant parties (GP, other departments / hospitals where the patient attends for care, the patient, and the data management team).

SPECIFIC ASPECTS OF CARE

Abdominal / Hepatobiliary

Patients with SCD may experience abdominal pain for several reasons some unrelated to the disorder (for example acute appendicitis). Careful examination and investigation will help to determine the cause and allow appropriate management. Patients with liver dysfunction should be investigated for both sickle related and unrelated causes of disease.

Abdominal pain can lead to hypoventilation which increases the risk of acute chest syndrome (ACS), it is important that should the patient be attending acutely that the *Acute Presentation* guidance is followed (12.1) with the patient receiving adequate, timely and appropriate pain relief.

Hepatobiliary complications common in SCD and have a multifactorial aetiology. Depending on the nature of the problem, referral to a specialist centre with expertise in sickle hepatopathy may be appropriate. In progressive liver disease, treatment may include an exchange transfusion programme and liver transplantation can be considered for highly selected patients with end stage liver disease.

Additional investigations to Section 12.1 that may be helpful:

- Conjugated and unconjugated bilirubin, ALT, GGT, amylase.
- AXR if abdominal symptoms include signs of distension or there are abnormal bowel sounds. It may also show constipation.
- Abdominal ultrasound / doppler to evaluate liver, identify gallstones.
- MRCP

- Viral serology and/or viral PCR including HAV, HBsAg, HBcAb, HCV, HEV.
- Screen for G6PD if result not already available.
- Autoantibody screen
- Hepatobiliary imaging.

Diagnosis to consider:

Acute intrahepatic cholestasis is a rare but severe form of sickle hepatopathy with a high fatality rate. It is caused by sickling within hepatic sinusoids, leading to vascular stasis, hypoxic damage and can lead to acute hepatic failure. There is tender hepatomegaly, hyperbilirubinaemia (predominantly conjugated) without evidence of extrahepatic biliary obstruction, coagulopathy and thrombocytopenia. Transaminitis, if present is mild or moderate. Exchange transfusion should be considered early. This syndrome has a high fatality rate; early exchange blood transfusion may be helpful.

Gallstones are common (over 70% of adults with SCD) due to the increased rate of haemolysis, resulting in pigment gallstones and/or biliary sludge. If asymptomatic, they do not require intervention. However acute cholecystitis characterised by right upper quadrant abdominal pain, fever, nausea and vomiting or ascending cholangitis can result, requiring intravenous antibiotic therapy, intravenous fluids, and analgesia. The investigation and management of patients with acute complications of gallstones should follow general treatment guidelines. Laparoscopic cholecystectomy should be considered for symptomatic gallbladder stones. It is important that the red cell team are aware of the presentation especially any plan for surgical intervention. Consider AXR, ultrasound or MRCP after discussion with gastroenterologist. Laparoscopic cholecystectomy should be considered for symptomatic gallbladder stones. Ursodeoxycholic acid should be considered in patients with chronic cholestasis.

Hepatic sequestration occurs when blood pools within the liver, resulting in tender hepatomegaly, worsening anaemia and jaundice. It is often associated with infection and thus requires intravenous fluids, analgesia and antimicrobial therapy. Top up transfusion to the patient's baseline haemoglobin can be considered in acute hepatic sequestration with anaemia.

Iron overload leading to liver failure is rare since the routine use of ARCE and iron chelation medication. As ferritin is an acute phase reactant in the blood test acutely ill patients with SCD will often have high ferritins for reasons unrelated to iron metabolism; it is more useful to request iron and transferrin saturations tests. Patients on blood transfusion programs should be offered 1 to 3 yearly R2 MRIs to determine any iron loading in the liver. Any patient with R2 showing >7mg/g dry weight should have urgent review of treatment and iron chelation protocol.

Jaundice in sickle cell disorders, is often due to an unconjugated hyperbilirubinaemia secondary to haemolysis and is painless. Hydration is recommended. Unconjugated hyperbilirubinaemia can also be caused by G6PD deficiency which is particularly relevant in SCD patients because of the risk of severe anaemia as a result of haemolysis, and by Gilbert's syndrome, which is a conjugation disorder and virtually harmless apart from the increased risk of gallstones. However, jaundice may be an indicator of hepatic or biliary disease.

Liver disease Patients with progressive liver disease should be considered for exchange transfusion programmes under the supervision of a specialist services. Liver transplantation in SCD should be considered in highly selected patients via HCC / NHP and multidisciplinary specialist teams. Liver biopsy should only be considered in cases of genuine diagnostic dilemma and should be done via the trans-jugular route to minimise bleeding risk.

Mesenteric / girdle syndrome is caused by sickling / slow flow or obstruction within the mesenteric vessels leading to pain, abdominal distension and quiet bowel sounds. An AXR may show dilated bowel loops and / or lactate may be raised. This may mimic an acute, surgical abdomen, but requires conservative management with analgesia, intravenous fluids, nil-by-mouth, +/- nasogastric tube, +/- oxygen therapy. If there is no improvement with conservative measures, exchange transfusion should be considered.

Splenic sequestration occurs when blood pools within the spleen, resulting in tender splenomegaly, worsening anaemia which can progress rapidly to hypovolaemic shock. This occurs most commonly in infancy but can occur in adulthood. Urgent top-up blood transfusion is usually required. The blood transfusion department should be informed to ensure blood is available and ready as soon as splenic sequestration is suspected. Consider referral to surgeons for splenectomy.

Viral hepatitis follows a similar course as in those without sickle cell, with raised transaminases and bilirubin. Although very rare HBV and HCV may be transmitted by blood transfusion and so HBV immunisation and regular hepatitis serology is recommended in those receiving blood transfusions; viral screen (HBsAg, HBsAb, HBcAb, HCV and HIV) is usually undertaken as part of the comprehensive annual review. Acute viral hepatitis requires referral to a local hepatologist. Fulminant hepatitis or liver failure requires management of a multi-disciplinary team including red cell haematologists and specialist hepatologists. Liver biopsy should only be considered in cases of genuine diagnostic dilemma and should be done via the trans-jugular route to minimise bleeding risk.

Circulation / Pulmonary / Cardiac

Acute Chest Syndrome

Acute Chest Syndrome (ACS) is defined as an acute illness with fever and / or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray. It is the **leading cause of death** and is unique to SCD often mimicking bacterial pneumonia. Early recognition and prompt treatment is critical**.**

Clinical features

New onset hypoxia is an early indicator. **Simply providing the patient with oxygen in order to improve the O2 saturation without further assessment is a critical error** and may result in lack of escalation of care.

The clinical features of ACS include (absence does not exclude):

- Shortness of breath
- Pain (often pleuritic) in chest wall, sternum, upper abdomen and / or thoracic spine.
- Wheezing and / or haemoptysis.
- Productive or non-productive cough.
- Fever and / or rigors.
- Tachypnoea, tachycardia.
- Falling oxygen saturations on air (< 94% or >4% fall from baseline) or oxygen requirement of > 4L to maintain SpO2 >94%.
- Signs of lung consolidation; usually bilateral and generally basal.
- Chest xray changes (typically bi-basal and symmetrical but may be unilateral). – **note clinical symptoms precede radiological changes in most cases**

Assessment and Investigations:

- In addition, to assessment and investigations in acute presentation (**Section 12.1**)
    - Nose and throat swab for respiratory viruses in patients with coryzal symptoms.
    - Consider urine for pneumococcal and Legionella antigen,
    - Consider nasopharyngeal aspirate for chain reaction (PCR) for viruses,
- CXR on any patient with signs of hypoxia **but this must not delay urgent clinical management** if the patient is very unwell or has rapidly progressive respiratory deterioration.
- Arterial blood gases on room air or oxygen if O2 saturation falls < 85%.

Notable investigation findings:

- Evidence of systemic inflammation (leucocytosis, raised inflammatory markers).
- Evidence of haemolysis (acute drop in Hb, increased LDH and bilirubin).
- Drop in platelet count is an independent predicator of severe ACS.
- Alveolar consolidation on chest xray.

Consider:

- Pulmonary embolism, if suspicion of PE and ACS treat for both simultaneously.
- Fluid overload; while hydration is important over hydration my lead to pulmonary oedema. Attention to fluid balance is important. Should be considered if patient deteriorates following blood transfusion. Of note, many patients with a severe VOC will present with pretibial oedema which is a consequence of sickling rather than indicative of fluid overload; overuse of furosemide should be avoided unless there are other features of fluid overload.
- Opiate toxicity; careful attention to avoid opiate toxicity in ACS, respiratory rate, sedation and pain scores must be carefully monitored.

- Hypoventilation due to pain: Chest splinting due to chest or thoracic spine pain may lead to atelectasis and precipitate or aggravate acute chest syndrome. It is essential that pain relief is effective.

Management:

The immediate aim of treatment in ACS is to prevent or reverse acute respiratory failure. Patients should receive care as indicated in **'Acute presentation' Section 12.1**; in addition:

- Liaise with high dependency /intensive care unit even in mild cases, as clinical deterioration is often rapid and unexpected (see **Appendix 2 and 4** for contact details). If LHT consider ICU / HDU management from outset and transfer to a SHT.
- Involve senior member of the red cell team as soon as ACS is suspected (see **Appendix 2** for contact details).
- Ensure blood transfusion laboratory is aware that a SCD patient has a suspected ACS, that a valid sample is available and that at least eight to ten units are available.
- Ensure patent suitable venous access; ideally two pink (20g) venflon, ARCE requires inlet and outlet, discuss and consent patient for possible blood transfusion.
- Not all patients with ACS will require a blood transfusion and the decision to transfuse can be complex, particularly if the patient has red cell antibodies. While there are no randomised controlled trials, there is observational and case control evidence for the efficacy of transfusion and it can be lifesaving in severe cases. **Key is prompt transfusion once decision made** therefore it is essential that the laboratory is aware units are ready, the patient has suitable venous access and has consented. The degree of hypoxia and respiratory compromise partly governs the need for and mode of blood transfusion. A senior member of the red cell team must be involved in the decision making. **Prompt transfusion, rapidly reducing the circulating haemoglobin S%, often results in a good response.** ARCE or manual exchange is ideal but if starting Hb allows top up transfusion aiming for a **post transfusion of no more than 100 g/l** means treatment can start quickly (see section on Treatment: Blood Transfusion Section 13.13).
- Oxygen therapy: Maintain SpO2 ≥ 95% or within 3% of the patient's baseline. Bronchodilator therapy may help, and NIV (CPAP or Optiflow) may be required.
- Chest physiotherapy and incentive spirometry (see **Appendix 6**) coupled with effective pain relief has been shown to be beneficial in younger patients by reducing chest splinting and is likely to be a useful adjunct to other forms of therapy. In severe cases chest physiotherapy should be initiated promptly.
- Antimicrobials: treat empirically for severe community acquired pneumonia, unless there are clinical data to suggest an alternative infection. Choice of antibiotic will be guided by local policy. Liaison with microbiology if unsure or in penicillin allergic patients (see **Appendix 2** for contact details).

Acute anaemia / Hypovolemia

Acute anaemia in SCD can progress rapidly and it is important to be aware of the causes and to recognise them early. Baseline Hb varies between genotypes and individuals, typically between 60 and 90 g/l in HbSS, higher in other genotypes for example HbSC usually above 100g/l. Steady state, baseline Hb's, are well tolerated and do not require transfusion therefore it is essential to be aware of the patient's baseline Hb which is available on the sPCP. While reticulocyte counts are usually higher than the normal range the count can be helpful in identifying the cause of the anaemia (a low count indicating failure of production and a high count suggestive of increased consumption). Causes of acute anaemia:

- Aplastic crisis most often caused by Human Erythovirus (Parvovirus) B19. The characteristic 'red' cheek is not always present and can be hard to recognise, often patients present with a non-specific viral illness. Patient should be isolated and close household members should have serology and an FBC sent if they also have a haemoglobinopathy or are pregnant
- Acute splenic or hepatic sequestration (discussed above under Abdominal / Hepatobiliary) characterised by crashing Hb, circulatory collapse with rapidly enlarging, painful spleen or liver.
- Haemolytic transfusion reaction (acute, delayed or hyperhaemolysis).
- Exacerbation of background haemolysis; severe sickle cell crisis; ACS, acute multi-organ failure, severe sepsis.

In addition to investigations outlined in 'Acute Presentation' (**section 12.1**) note size of spleen and liver, obtain urine sample for HPLC if patient transfused within the last three months and transfusion reaction suspected along with urgent samples to be sent to the blood transfusion laboratory; septic screen including virology and atypical serology and human erythovirus (parvovirus) serology.

Management

Management will depend on cause and cardiovascular compromise. Transfusion management must be discussed and agreed with the patient, a senior member of the red cell team and the blood transfusion laboratory. On the background of a potential haemolytic transfusion reaction the risks may outweigh any benefits; further advice can be sort from NHS Blood and Transfusion Consultants. Rapid changes in blood viscosity may increase the risk of stroke therefore it is important to use a slow transfusion rate if possible.

Leg Ulceration

Leg ulceration is a frequent and disabling complication of SCD. Once they occur they may persist for months or years and are associated with severe chronic pain and recurrence is frequent. Leg ulceration is possibly linked to haemolysis/endothelial dysfunction rather than veno-occlusion. In addition, mechanical obstruction, high blood viscosity, venous incompetence, hypercoagulability and thrombosis may also play a role in the development of ulcers. These factors place patients at higher risk of developing ischaemia and once tissue damage occurs the cycle repeats leading to further tissue damage with fluid retention and inflammation encouraging ulcer formation and limiting healing. A multidisciplinary approach is necessary and treatment may include both local wound care and systemic treatments (see **Appendix 4** for tissue viability service and microbiology contact details).

Recommendations:

- Patients with leg ulceration should be treated by a multidisciplinary team which includes wound care experts.
- Patients with sickle-related leg ulcers should be assessed for venous insufficiency with venous reflux studies.
- Multi-component compression bandaging should be offered, particularly in patients with evidence of venous insufficiency.
- Dressings directed at inhibiting/modulating matrix metalloproteinases can reduce healing times and may be recommended by wound care experts.
- Check zinc levels and provide supplements to those with deficiency.
- Patient education is a vital part of ulcer management and advice should include:
    - Eating a nutritious and well balanced diet.
    - Avoiding injury, especially to feet, ankles and legs.
    - Avoiding dry skin by using local moisturisers.
    - Wearing socks and well-fitting shoes.
    - Using insect repellents and protection against insect bites.
    - Treating minor trauma around the ankles quickly.
    - Avoiding blood tests or intravenous line insertion in the lower limbs.
    - Consider wearing compression stockings.
- Patients with SCD-related leg ulcers should be offered appropriate analgesia and may require support from a specialist pain team. Regional nerve blocks may be of benefit.
- A trial of blood transfusion therapy could be considered in patients with intractable leg ulcers.
- Leg ulcers may be caused by hydroxycarbamide therapy, stopping therapy may be required to facilitate wound healing.

Pulmonary Disease

90% of adults with HbSS have abnormalities in lung function. It is important to obtain medical history with information on smoking, asthma, episodes of ACS, episodes of pneumonia and occupational history

to ensure that whole picture is obtained. Chronic lung disease can result from recurrent acute chest

syndromes, or thromboembolic disease, but can also arise in the absence of previous clinical episodes with low baseline oxygen saturations or worsening dyspnoea on exertion. Patients of concern should be referred to the respiratory team (see **Appendix 4** for contact details). There are four stages of disease (see **Appendix 5**) it is not clear whether patients progress through the stages or whether early intervention is of benefit.

Investigations:

- All patients attending acutely should be assessed for respiratory symptoms and respiratory examination must occur in outpatients at a minimum of yearly during the annual comprehensive review.
- As in 'Acute Presentation' guidance (**Section 12.1** oxygen saturation (SpO2) on air should be noted and compared to baseline recorded in the patients sPCP.
- Routine Pulmonary Function tests in asymptomatic adult patients are not recommended.
- Patients with respiratory symptoms or chronic hypoxia should be investigated with:
    - Spirometry with transfer factor
    - High resolution computerised tomography (CT) of the lung
- Patients should be referred for a sleep study if:
    - self-reports of disturbed sleep
    - excessive daytime sleepiness (Epworth sleep score >10)
    - oxygen saturations awake <95%
    - a history of snoring, priapism or early morning headaches.
- Patients with suspected chronic lung disease or abnormal sleep studies should be referred to a respiratory physician for review and consideration of therapy (see **Appendix 4**).
- Consider ECG and / or ECHO, it is important to perform ECHO 1 to 3 yearly as part of the outpatients annual comprehensive review to screen for pulmonary hypertension.

Management:

- Prompt treatment of chest infections
- Advice on smoking cessation
- Home oxygen therapy when appropriate
- Referral to respiratory team with a specialist interest in SCD.

Pulmonary Hypertension

Pulmonary hypertension (PH) has been reported in 6-11% of adult patients with SCD. The causes are multifactorial and include chronic intravascular haemolysis leading to reduced nitric oxide scavenging, left sided heart disease, chronic lung disease, chronic thromboembolic disease, pulmonary vascular disease, hypoxaemia, oxidant stress and asplenia. PH in SCD is associated with increased age, poor functional capacity, prior history of cutaneous leg ulceration, anaemia, higher N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, renal insufficiency and markers of haemolysis.

Investigations:

Doppler echocardiography is the mainstay of identifying pulmonary hypertension. A useful algorithm for a screening strategy is given below:

- Baseline ECHO:
    - Normal ECHO repeat ECHO in three years.
    - Raised TRV but no RHC repeat ECHO annually.
    - Raised TRV > 290 cm/sec refer to pulmonary hypertension specialist.
    - Raised TRV 250-290 cm/sec with raised NT-proBNP or reduced 6MWT.

Management:

- Referral to PH specialist (see **Appendix 4**) if TRV >290 cm/sec and if raised TRV 25-290 cm/sec with raised NT-proBNP or redcued 6MWT.
- Patients with PH should be evaluated for thromboembolic disease, chronic lung disease, hypoxaemia, sleep-disordered breathing, HIV infection and autoimmune disease.
- Consider disease modifying treatment, aiming at improved anaemia and reduced haemolytic rate.

- Under direction of PH specialist start on medication.

Endocrinopathies / Endocrine

From childhood, delayed growth and puberty is a common finding in both males and females. In adult males, hypogonadism can occur and semen analysis may show decreased total sperm counts (oligospermia), reduced motility, and reduced indices of semen quality. Osteopenia and osteoporosis can also occur and is often multifactorial. Transfusional iron overload can also lead to endocrinopathies but these occur infrequently in patients with sickle cell disorders compared to those with the thalassaemia syndromes.

Investigations:

- LH, FSH, testosterone / oestradiol, PTH.
- R2 MRI scan of liver.
- Bone mineral density scan (DEXA).
- Consider early morning cortisol levels.
- Consider screening for diabetes melitus in patients at risk of cardiovascular disease.

Management:

- Referral to specialist endocrinology services (see **Appendix 4**) for patients showing abnormal results.
- Chelation for transfusional iron overload.
- Bisphosphonate therapy and lifestyle modification for bone thinning.
- HbA1c is not a valid test in patients with SCD; alternative tests such as an oral glucose tolerance test for diagnosis of diabetes or serum fructosamine for monitoring trends

Infection

Sickle cell patients are functionally hyposplenic and are usually on long-term prophylactic antibiotics. If unwell low threshold antibiotic treatment is appropriate, as per trust protocol. If there is no clear source of infection but patient is pyrexial ensure a septic screen and commence broad spectrum antibiotics. Patients with SCD are prone to unusual infections; pneumococcal septicaemia, haemophilus influenzae, salmonella (which can cause osteomyelitis and septicaemia), staphylococcal osteomyelitis, mycoplasma pneumonia, E coli UTI and parvovirus (which can cause aplastic crisis). The reader should refer to local guidance on antibiotic use and involve Microbiology for advice in complex cases or those that are allergic to penicillin (see **Appendix 4**).

Investigation

Additional samples according to local policy (microbiology and antibiotic use) may include:

- Parvovirus, Mycoplasma serology, Legionella, Hepatitis serology, HIV, Pneumococcal, Yersinia (particularly if on Desferrioxamine).
- Stool or sputum.
- Blood cultures
- Urine dipstick and / or MSU+C
- Swabs (throat, viral, wound etc)
- Malaria if recent travel.

Management

Patients with SCD should be on prophylactic dose oral phenoxymethylpenicillin (Pen V) 250mg twice a day. If allergic to penicillin oral erythromycin 500mg mg twice a day. The Pen V can be increased to 500mg four times a day when unwell with a temperature >38°C. To reduce the risk of other complications it is important to identify and treat infection quickly and aggressively. Management and antibiotic use should be in line with local policy. **Patients on the iron chelator desferrioxamine** who have diarrhoea and / or abdominal pain should stop treatment and be **started immediately on iv ciprofloxacin** until *Yersinia* has been excluded.

Vaccinations

All patients with SCD should be strongly advised to receive all routine vaccinations available and to ensure that they are kept up to date. As they are functionally hyposplenic it would be recommended that they also receive:

- Pneumococcal vaccination (the exact formulation and timings in line with national policy).
- Annual influenza vaccination
- Hepatitis B vaccination in line with national guidance and local policy.
- COVID 19 vaccination and boosters.

Mental Health

Patients may present with mental health problems / issues either acutely or via outpatients which may not be related directly to their SCD. Acute mental health crisis should follow general support and local guidance, but it is important that the red cell team are informed and are involved in order that generic aspects of their SCD can continue, particularly should the patient require in-patient services.

Psychological Support

SCD is a lifelong, life limiting inherited blood disorder and it is essential that the patient feels supported in all aspects of their care. Chronic pain and episodes of acute pain can result in the long-term use of hospital services and it is essential that trust is maintained and that the patient is supported in all aspects of their care. Access to specialist psychological support around how to engage and comply to difficult and challenging prevention and treatment protocols is essential. Local and national data suggests that health care provides often have misperceptions about patients living with SCD. In addition, patients can face societal discrimination and stigmatisation leading to loss of self-esteem and entrenched chronic shame. Socio-economic difficulties are common as is completing education and maintaining employment. The role of stress, depression, fear and anxiety are key areas that require understanding and support from specialists in the care of SCD. At a minimum all patients with SCD should receive yearly assessment of their mood as part of their comprehensive annual review. Depending on the score and / or concerns the red cell team should encourage engagement with the psychology services provided (see **Appendix 2** and **4** for contact details).

The role of the red cell psychology service is to provide:

- psychological and / or neuropsychological assessment as required.
- psycho-education and evidence-based therapy, including CBT.
- support to patients and families transitioning to the adult services.
- Input, as required, at the comprehensive annual review by identifying patients with poor mood, quality of life and coping scores.
- Provide patient input at MDT meetings and inpatient ward rounds.

Neurology / Neurological Complications

Central nervous system (CNS) complications in adults with SCD cause significant morbidity and mortality. Acute presentations can include headache, seizures, focal neurological signs, visual impairment, altered consciousness and deterioration in cognition; aetiologies include stroke and infection. Early recognition of acute neurological complications is vital, alongside rapid diagnosis and appropriate management. A summary flow chart is provided **Appendix 15.**

Headaches

Recurrent headaches and migraines are common in SCD and require evaluation including measurement of vital signs: blood pressure and heart rate, neuroimaging of the brain and cerebral vessels, and referral to a neurologist if the symptoms persist.

Intracranial aneurysms and moyamoya disease

Some patients with SCD develop a cerebral vasculopathy, including stenosis of the supraclinoid carotid arteries causing a moyamoya syndrome. Intracranial aneurysms are more common in SCD, especially in HbSS. Women between the age of 30 – 39 with SCD are at greater risk of aneurysmal subarachnoid

haemorrhage. The management of small asymptomatic aneurysms is unclear and does not justify routine screening however all SCD patients with new onset should have further investigation.

Stroke

Stroke is a severe/life-threatening complication of SCD. Stroke may be ischaemic due to occlusion of cerebral arteries or haemorrhagic due to aneurysmal rupture or bleeding from Moya Moya vessels. However, particularly in older patients, consideration should be given to the primary cause being unrelated to sickle cell, for example thrombophilia, CNS infection, illicit drug use, arterial dissection and congenital heart disease. Strokes have long-term effects including neurocognitive and neuropsychological dysfunction. There is little evidence on the assessment and management of stroke in adults with most treatment strategies being extrapolated from paediatric data.

Symptoms and signs of stroke

Characteristically patients present with hemiparesis and / or paraesthesia (limb, facial weakness or slurred speech), but other neurological symptoms such as severe headache, seizures, decreased consciousness, acute confusion and/or behavioural change may occur. Transient ischaemic attacks can predict stroke.

Investigation

In addition to investigations outlined in **Acute Presentation Section 12.1** the following should be considered**:**

- MRI brain, CT head and MR angiography.
- ECHO
- ECG
- Lipid screen
- Thrombophilia screen on advice of a consultant haematologist

Differential Diagnosis:

The differential diagnosis to either ischaemic or haemorrhagic stroke includes:

- Focal neurologic deficit.
- Hemiplegic migraine.
- Seizures.
- Posterior reversible encephalopathy syndrome (PRES): defined as a reversible clinical–radiologic syndrome, with patients presenting with a constellation of symptoms, including headache, seizure, visual disorders, and altered mental status, and supported by imaging findings that show parietal and occipital involvement of the brain, likely resulting from vasogenic oedema. PRES can be associated with ACS and has been linked sporadically to blood transfusion. Evidence exists that not all cases of PRES are reversible, nor do they always involve the posterior brain.
- Cavernous Sinus Venous Thrombosis (CSVT) is a less common neurologic complication in SCD when compared with ischemic strokes. Despite the low frequency, detecting the presence of CSVT is important because its presence may alter the treatment strategy. Patients with SCD and CSVT can present with symptoms that mimic a stroke, such as seizures, coma, cranial nerve palsies, headaches, nausea, and vomiting. An evaluation with a MRV is the preferred initial imaging study because the imaging sequence only adds a maximum of 7 minutes to the initial MRI to detect an ischemic or haemorrhagic cerebral infarct.

Management

Patients presenting acutely within 4 hours of the onset of symptoms should be transferred directly to the Hyperacute Stroke Unit (HASU), see **Appendix 2** and **Appendix 4** for contact details and **Appendix 15** for summary flow chart of actions. The red cell team at the tertiary unit should arrange an urgent red cell exchange. Those presenting with symptoms of longer duration should also be discussed with HASU. If transfer to HASU is not deemed appropriate, ensure patient is stable and organise urgent CT scan of the brain. If the CT is performed within 24 hours of the onset of symptoms, there may be no evidence of ischaemia or changes may be subtle. Urgent discussion with and referral to a neurosurgical unit is required if there is evidence of cerebral or subarachnoid haemorrhage. Urgent red exchange transfusion is required unless this will delay transfer to a neurosurgical unit. If there will be a delay in obtaining the volume of blood required for the exchange transfusion and the patients Hb is below, consider initial top-up transfusion up to 100 g/l under guidance of senior member of the red cell team.

Standard management and stroke prevention should include:

- Management of modifiable risk factors such as systemic hypertension, hyperlipidaemia and / or atrial fibrillation.
- Advice on smoking cessation.
- Consider anti-platelet therapy in line with national stroke guidance.
- Patients who have been started on regular blood transfusion therapy for primary stroke prevention during childhood should be assessed on transition to the adult service by a red cell haematology consultant who should offer continued transfusion or hydroxycarbamide if they have had abnormal TCD and there is no evidence of vasculopathy.
- All patients who have had a sickle related ischaemic or haemorrhagic stroke should be on an indefinite transfusion program. The recurrence rate of ischaemic stroke is very high without transfusion. Hydroxycarbamide should be considered in patients where transfusion is not possible or acceptable.
- Silent cerebral infarcts may have effects on IQ and cognitive performance, including memory. Patients with neuro-cognitive defects should receive investigation with MRI/MRA scans and neuropsychological testing. Referral for support from the red cell specialist psychologist (**Appendix 2**) should be discussed with the patient and recommended.
- Seizures are common after stroke or subarachnoid haemorrhage. Review opioid use / dose and consider anticonvulsive (diazepam either PR or iv). If the seizures are on-going neurology expert input along with HCC MDT discussion would be recommended.

Ophthalmology / Ocular Complications

Complications can occur in up to 50% of patients most frequently in HbSC. Sickling within the vascular bed of the eye can lead to proliferative or non-proliferative sickle retinopathy. In non-proliferative retinopathy characteristic findings are seen on ophthalmoscopy, but they are not associated with visual impairment. In contrast proliferative retinopathy can lead to vitreous haemorrhage (Stage IV) or retinal detachment (Stage V) with visual impairment. Patients with sudden visual deterioration should be seen within hours in Eye Casualty (see **Appendix 4**). Patients should be made aware that any trauma to the eye requires urgent ophthalmological review. Ischaemic and haemorrhagic stroke can also lead to acute visual loss. Endophthalmitis is a rare septic disorder than can cause acute visual loss and requires urgent antibiotic treatment for sepsis. Laser photocoagulation therapy for eyes with proliferative sickle cell retinopathy (PSR) may prevent visual loss and vitreous haemorrhage and would be considered by the specialist centre if appropriate. The role and frequency of regular ophthalmic screening is uncertain and there may be a benefit of targeted screening for those patients who are most likely to develop visual loss. Another frequent finding in SCD is temporal thinning of the retina by Optical Coherence Tomography (OCT), likely representing ischemic retinal atrophy from occlusions of the retinal circulation. There is currently no evidence that disease modifying treatment can reverse or prevent either proliferative sickle cell retinopathy or ischaemic retinal atrophy.

Recommendations:

- Management will be via the specialist ophthalmology service (see **Appendix 4**).
- Patients with SCD should be treated by ophthalmologists with sub-specialty expertise in retinal disorders and SCD.
- Patients on desferrioxamine or deferasirox should also be monitored for visual problems due to the development of drug-induced retinopathy.
- Laser photocoagulation therapy should be considered for patients with proliferative sickle retinopathy.
- Screening recommendations
    - All patients with SCD should have a baseline retinopathy screening.
    - Follow up screening:
        - HbSS stage 0 or 1 retinopathy: every 5 years
        - HbSC stage 0 or 1 retinopathy every 2 years
        - Asymptomatic temporal thinning by OCT: yearly

- HbSC or HbSS stage 2, 3, 4 or 5 - review planned on individual basis as advised by specialist ophthalmologists.
    - Patients on desferrioxamine or deferasirox iron chelation for iron overload annually.

Orthopaedic Complications

The two most common orthopaedic complications of SCD include avascular necrosis (AVN) and osteomyelitis. Both conditions can cause chronic pain with the resulting consequences. Osteomyelitis can also mimic veno-occlusion and if in doubt, imaging should be requested. In addition patients may have accidents resulting in fractures due to trauma which should be treated in the same may as patients with a SCD however if the patient requires admission or surgery under a GA the red cell team should be informed. **Avascular Necrosis (AVN):**

Avascular necrosis occurs in approximately 10% of SCD patients (50% of patients with HbSS by the age of 33 years) mostly affecting the femoral and humeral head, although may affect other joints. It commonly affects multiple joints and in the early stages can be asymptomatic. AVN should be considered in patients presenting with sudden onset or progressive joint pain, especially in the hip or shoulder joints.

Investigations

- Patient history.
- Examination, limited movement particularly abduction and external rotation of the hip and / or shoulder.
- X-ray of joint, MRI should be considered if the plain X-ray is normal
- Diagnosis on Xray or MRI and referral to orthopaedic team for staging.

Stages for femoral head AVN (for information)

Early stage 0: No radiological sign although marrow necrosis may be present histologically.
Early stage 1: No radiological sign abnormal MRI with marrow and bone necrosis.
Early stage 2: Diffuse porosis, sclerosis or cysts on xray.
Transition: Femoral head flattening and crescent sign.
Late stage 3: Collapse: Broken contour of head, sequestrum, joint space normal.
Late stage 4: Osteoarthritis: Flattened contour, decreased joint space and collapse of head.

Treatment:

The treatment for AVN is dependent on the grade of joint involvement.

- In patients with early disease (stage 0-2) physiotherapy, pain management (local joint anaesthetic), activity modification and walking aids can be helpful. However these approaches will not provide long term relief / disease progression. Disease-modifying treatments (hydroxycarbamide, transfusion) may stop new AVN from developing but does not prevent disease progression.
- AVN stage 3 – 4 in SCD patients should be managed using a multidisciplinary team (MDT) approach involving senior members of the red cell team and a specialist orthopaedic surgeon (see **Appendix 4**).
- Core decompression can be considered in selected cases of non-collapsed femoral head early stages, in the hope that this will promote revascularisation and healing of the dead core. However, long-term results appear disappointing with the majority of patients eventually progressing.
- Total hip replacement is indicated in patients with persistent, intractable hip pain and disability affecting daily activities who have failed non-operative management.
- There are fewer studies reported for shoulder surgery in sickle patients. However good outcomes have been reported with regard to both arthroplasty and resurfacing surgery.
- Prior to joint replacement surgery it is essential that there is an agreed plan. The anaesthetic, surgical, pain management and red cell team should be involved in the preoperative management.
- Post-operative infection prophylaxis and thromboprophylaxis are recommended unless contra-indicated.

- Major joint arthroplasty surgery should be carried out in centres experienced in managing patients with SCD.

Marrow Fat Embolism Syndrome

Fat embolism syndrome (FES) resulting from extensive bone marrow necrosis (BMN) is a rare but potentially underdiagnosed and probably the most devastating acute complication of SCD. It is characterized by acute respiratory failure, neurological manifestations, thrombocytopenia, and multi-organ failure. **The mortality rate is very high**. Its association with milder forms of SCD may lead to late

diagnosis or under-recognition. Cases of "multiorgan failure syndrome" affecting previously well patients

who deteriorate rapidly after presenting with a seemingly uncomplicated painful crisis may represent cases of FES. All patients attending acutely should be monitored in line with 'Acute Presentation' guidance (section 12.1) for any critical warning signs. The syndrome can be mistaken for ACS, stroke or other conditions. Early examination of the peripheral blood film by senior staff is essential.
Given the respiratory and neurological manifestations, the syndrome can be mistaken for isolated ACS or stroke whereas the combination of fever, neurological manifestations, and thrombocytopenia may suggest a diagnosis of thrombotic thrombocytopaenic purpura or even acute leukemia if the cytopaenias are severe. Examination of the peripheral blood smear is essential.

Investigations

- Patient monitoring for signs of hypoxia, petechiae and neurological abnormalities
- Examination of peripheral blood film
- LDH and Serum ferritin

Diagnosis

- Dyspnea, tachypnea and hypoxia
- The peripheral blood smear shows a leukoerythroblastic picture with circulating nucleated red blood cells (NRBCs)
- Extremely high serum ferritin and lactic dehydrogenase (LDH)

Management

Treatment should be in ITU with full support and treatment for sepsis. In case of liver failure, early transportation to a tertiary liver unit (with on-site red cell services) should be considered.
The mainstay of specific treatment is rapid red cell exchange transfusion, preferably automated. There is limited evidence that an additional plasma exchange (1 volume) may be of possible benefit in reversing the multi-organ failure. It is important to have an early urgent discussion with HCC via MDT (see **Appendix 2** and **Appendix 14**) re: management of suspected cases of fat embolism syndrome.

Osteomyelitis

Osteomyelitis can arise as a result of septic emboli. Salmonella, Staphylococcus Aureus and other gram-negative enteric bacilli are the most common causes of osteomyelitis. Tuberculosis has also been reported to cause osteomyelitis in SCD. It is likely that pre-existing AVN increases the risk of osteomyelitis as a result of the reduced clearance of micro-organisms and debris from bone dead space. Chronic osteomyelitis, especially when low-pathogenic micro-organisms are involved, causes pain but may not necessarily present with systemic symptoms and/or a raised CRP. In addition to 'Acute Presentation' **Section 12.1**:

Investigation

- Focal local tenderness, warmth, bone swelling and fever.
- Patient reports pain feels different to usual VOC.
- Bloods for inflammatory markers.
- Blood cultures should be taken in patients with ongoing bone pain and/or fever where a clinical diagnosis of osteomyelitis is suspected.
- In selected cases, MDT with red cell and orthopaedic specialists, radiological examination (MRI) or bone biopsy/aspiration should be considered to confirm the diagnosis. USS can show increased subperiosteal fluid (>4mm).

Treatment

- Treatment of osteomyelitis should be with a prolonged course of an antibiotic appropriate to cover the organism isolated.

- If a large AVN is involved, a multidisciplinary approach is desirable exploring if surgical options (debridement, dead space control, local antibiotics) may be indicated.

Management

- Start antibiotics (eg ceftriaxone).

- Early involvement of Microbiology.
- Accumulation of fluid may require drainage.

Outpatient management and annual review

Patients with SCD should be monitored for the specific complications so that early treatment regimens can be instigated. At a minimum all patients (HbSS, HbSC, $HbSb^0$ or other rarer clinically significant genotypes) must be offered a comprehensive annual review by a senior member of the red cell team with the results submitted onto the NHR. Where possible, adults with SCD should be offered care close to home and with the minimum disruption to work / further education as possible, although this needs to be balanced against access to specialist care and local arrangements. The necessity and frequency of follow- up outpatient appointments will vary from patient to patient and within the lifetime of individuals depending on need. However, outpatient engagement is key to the long-term care with early detection of potential complications, problems and issues with treatment an essential aspect of keeping patients living with SCD as well as possible.

Annual Review

- Each patient should have a comprehensive annual review (see **Appendix 11**) for a proforma that can be completed in outpatient clinic. The proforma ensures thorough and consistent care in line with national standards.
- The annual review appointment will take longer than a routine outpatients appointment and this must be reflected in the time allocated. The number of annual review appointments available must match the number of patients living with SCD that the hospital serves. The format of the appointments will be determined locally and may be offered via attendance at a SHT or as outreach.
- Each hospital must have local arrangements to ensure that a copy of the annual review proforma or the resulting letter is forwarded to the red cell data management team (**Appendix 2**) to be uploaded onto the NHR. This data forms the basis for the continuous clinical governance of the service.
- In line with local practice it is recommended that outpatient letters outlining all the information from the annual review is sent to the patient and their GP. This letter can be used by patients as evidence of their condition, treatment(s) and any complications to support PIP (Personal Independent Payments) applications, housing, further education or employers.

Data and Service Management

- Each individual hospital has access to a red cell data manager (see **Appendix 2** for contact details).
- Each individual hospital must maintain an inventory of patients with SCD to ensure follow up and comprehensive annual review with a senior member of the SHT.
- Each individual patient should have a record on the NHR (there is a process for anonymising data, via the NHS number, should the patient wish to opt out). The NHR provides national data and can be accessed by red cell team (https://nhr.mdsas.com/).
- Services should participate in a quality review programme of haemoglobinopathy services against nationally agreed standards (https://haemoglobin.org.uk/3d-flip-book/health-services-for-people-with- haemoglobin-disorders-standards-2021/).
- Local, SHT, HCC and NHP meetings:
  - All adverse incidents and events should be taken to and discussed at red cell SHT MDTs (Proforma available **Appendix 14**) and then at HCC or NHP as required / decided.
  - Complex cases and cases where novel treatment regimens (see section below) might be clinically appropriate (for example stem cell / bone marrow transplantation, use of voxelotor).

General Outpatient appointments

- Some patients will need to be seen regular particularly if they are on regular treatment, for example ARCE, hydroxycarbamide, for routine blood monitoring or be offered follow up appointments following inpatient stay.
- There will be local arrangements for which patients these patients should be booked (**Appendix 4**).

- It is essential that a holistic approach is provided via outpatient appointments and patients may require support for in any and all areas of their life for example, housing, welfare, financial support and support for work and education. Services must have local arrangements to provide a service within these and other areas. Details of who to contact are provided in **Appendix 4** a template letter in **Appendix 8**.

Planned, elective, surgery in SCD patients having a General Anaesthesia

Administration of general anaesthesia (GA) to patients with SCD carries an increased risk of perioperative complications. The TAPS trial (Howard J et al, The Lancet, 2013) showed that preoperative transfusion was associated with decreased perioperative complications. Complications are less likely with spinal or epidural anaesthesia and unless patients have very severe phenotypes or are very anaemic, this group is unlikely to need pre-operative transfusion. **Tourniquet surgery is a very high-risk procedure, even in asymptomatic carriers (HbAS) and should be avoided where possible.** The following protocol aims to provide guidance on the perioperative management of patients with sickle cell disease to minimise complications. A summary is provided in **Appendix 13**.

Accountabilities and Responsibilities

- The surgical / preoperative assessment team must inform the Red Cell team as soon as possible when a patient with a SCD has been scheduled for a surgical intervention (**Appendix 2**).
- The patient should be advised that before a date for surgery is set that a MDT perioperative management plan needs to be agreed between the surgical team, the red cell team and the patient.
- Each SCD patient scheduled for elective surgery under GA should be discussed at local SHT MDT (**Appendix 14**) and a management plan agreed taking into account the sickle genotype, complications, baseline Hb, baseline oxygen saturation, the length of the procedure, previous transfusion history and any allo-antibodies, antibiotic prophylaxis.
- The plan should be communicate to the surgical team and documented in the patient's records. The plan should outline any preoperative transfusion dates, an expected preoperative Hb and HbS%, plan for intraoperative / post operative transfusion, whether ICU / HDU bed may be required (postoperative care desirable for at least 24 hours) and suggestion for post operative pain relief (ie whether opioid naïve or tolerate who may require higher doses for effective pain control).
- Especially when a preoperative ARCE has been agreed, it is important that elective surgery **does not get cancelled or moved**.
- **Communication is paramount.** The surgical team and the red cell team share the responsibility of informing each other about the patient with SCD in theatre / on the ward.

Perioperative Measures

- Ensure **good hydration**. Patients will normally be fasted so it is important to prevent dehydration which can precipitate sickling. Commence iv hydration, for example alternating 1 litre of 0.9% sodium chloride and 1 litre 5% dextrose 6-hourly.
- Ensure good **oxygenation** (supplemental oxygen as indicated, aim at SO2>95%). Use of incentive spirometry is encouraged (see **Appendix 6**).
- Ensure patient is kept **warm, do not use ice packs for swelling**
- **Antibiotic prophylaxis**: Individuals with sickle cell disorders are prone to infection. If the operation carries an infection risk (e.g. gall bladder, ERCP, gynae, bowel operations) give prophylactic antibiotics in line with local policy, for example co-amoxiclav 1.2g i.v. with the pre-med, continue 8- hourly for at least 24 - 48 hours, converting to oral 625 mg po tds as soon as possible.

- **Continue other regular medications**
  - **Use thromboprophyaxis** according to Trust guidelines.

Travel advice and management

Patients with SCD may request advice regarding holidays and travel insurance. It is sensible to refer the patient to the Sickle Cell Society for advice. Patients should be encouraged to carry a copy of their last annual review so that they have information to provide to health care professionals should the need arise. Patients traveling on long haul flights can be discussed in local or SHT / HCC MDT (**Appendix 14**) as to whether pre flight / travel transfusion would be appropriate and / or to provide letters to be provided at security (example provided **Appendix 7**).

Pain Management

More information on pain in patients living with SCD is available in **Appendix 12**.

Chronic Pain

The PiSCES study (see references for link) suggested that a large number of patients living with SCD experience pain on a daily basis.

Characteristics of Chronic Pain:

- On the background of ongoing vaso-occlusion.
- Exacerbating/remitting course with periods of high and low pain.
- Secondary to avascular necrosis, leg ulcers, or other sequelae.
- Often no anatomic correlate to explain the pain.
- Nerve damage and chronic inflammation.
- Opioid use (hyperalgesia).

Problems related to long-term use of opioids:

SCD patients with chronic pain are often dependent on regular use of opioid analgesia for VOC (acute pain). Whilst the analgetic effect is often adequate, there are some serious problems with the long-term use of strong and highly dosed opioids (see **Appendix 12** for further information on pain).

Guidance on Management of Chronic Pain in SCD:

- Patients should have access to and be encouraged to attend the MDT Pain Service (see **Appendix 4**). The MDT Pain Service comprises of pain, psychology and red cell specialists. Individual programs for pain management will be discuss and agreed with therapeutic interventions such as CBT, physiotherapy, nerve blocks and management of the emotions associated with pain.
- Treat any underlying causes of pain including disease-modifying treatment (HU, transfusion) and local treatment of for example AVN.
- Apply principles of chronic pain management:
    - Patients with neuropathic pain should be offered appropriate analgesic medication.
    - Individual care plans should be considered for patients with complex care needs.
- Long-term opioid use should be regularly reviewed (at a minimum yearly as part of the patient's comprehensive annual review).
- All health care professionals involved in caring for SCD patients, including primary care, should be aware of prescribing plans.

Vaso-Occlusive crisis (Uncomplicated Painful Crisis)

Vaso-occlusive pain, typically severe, is the commonest reason for hospital admission and must be treated as an acute medical emergency. There is no specific test that confirms whether the patient is in a sickle cell crisis or not, regard the patient (and/or their carer) as an expert in their condition. Patients can usually differentiate what is sickle pain from what is not.

Follow instructions for 'Acute presentation' **Section 12.1** and summary **Appendix 3**. **Ensure adequate and timely pain relief and complications are excluded.**

Ensure that the sPCP (example **Appendix 10**) has been checked and pain relief is administered in accordance with the individual care plan. Listen to the patient, respect patient preference, ensure hydration, reassure, ensure physical comfort and emotional support.

General principle if key record not available give analgesia:

- Pain score less than 2 give paracetamol, non-steroidal anti-inflammatory (if not contraindicated), dihydrocodeine for mild and or codeine.
- Pain score greater than 2 as per sPCP or s/c morphine 0.15 mg/Kg hourly or oxycodone 5- 10mg s/c or diamorphine 0.1mg/Kg, depending on availability / patient tolerability. If on-going pain after 30 minutes give 50% of initial dose.
- Once pain is under control change patients onto oral analgesia as soon as possible, however it usual to continue with bolus subcutaneous pain relief, in line with above and availability / tolerability for at least the first 24 hours. This should be via PCAs if available. Of note some patients particularly those recently transferring from paediatric services should be able to and should be encouraged to move to oral immediate release morphine sulphate (Oramorph) as soon as possible.

Of note: in line with national guidance pethidine should be avoided as the metabolite norpethidine is known to cause seizures.

Renal complications

Patients with SCD often have a degree of renal impairment. The pathophysiology is complex and varies depending on each patient's disease phenotype. This can be best understood by remembering that the physiological conditions (oxygen pressure, pH, osmolality) vary markedly throughout the nephron – this leads to varying degrees of sickling and microvascular occlusion at different levels of the nephron, resulting in non-uniform, and seemingly contradictory at first glance, effects on renal function (e.g. there may be hyperfiltration of creatinine but reduced ability to maintain ion transport leading metabolic acidosis).

In essence, patients with SCD should be assumed to have poorer renal function than traditional laboratory tests indicate. It is therefore **important to always compare the creatinine level with baseline which is noted on the patient's sPCP**. Local reference ranges for creatinine should be interpreted with caution, with a low threshold to consider renal impairment. NSAIDs should be avoided in all patients with CKD stage 3 or worse and where available, drug level monitoring should be considered for renally cleared drugs with a narrow therapeutic index (e.g. antimicrobials) as the eGFR or calculated creatinine clearance is not reliable is SCD patients.

The natural history of renal impairment in SCD involves initial hyperfiltration in early childhood resulting in hyposthenuria, an inability to concentrate the urine. This makes patients susceptible to nocturnal enuresis (particularly in childhood) and dehydration/AKI, so maintenance of adequate hydration is important.

As individuals progress into early adulthood, many develop proteinuria, initially detected as microalbuminuria. This progresses to CKD in up to 1/3 patients by 30 years of age. The median age of progression to ESRF is 41 years (the classical histological appearance of which is focal segmental glomerulosclerosis); although the precise prevalence is not known, ESRF has been shown to the cause of death in >10% SCD patients.

Aggressive management of hypertension and proteinuria are cornerstones for preventing deterioration of kidney function.

A number of patients will experience additional complications which may expedite the progression of the renal impairment:

- **Acute infarct** (**renal papillary necrosis**), presenting as acute painless frank haematuria, in a similar manner to a stroke leading to a rapid decline in organ function.The focus of acute management is adequate hydration to minimise the risk of further infarction and ensure any clots are passed (if clots are not passed, they can complicate matters by causing obstructive uropathy).
- **Renal stones** (and **gout**) are common in the context of hyperuricaemia. Renal stones are likely to present as painful frank haematuria. Patients should be given adequate analgesia, with a low threshold for consideration of renal impairment due to obstruction.
- **UTIs** are common in SCD; recurrent UTIs can increase the risk of CKD. They should be aggressively treated to prevent progressive renal pathology. Antibiotics should be prescribed as per trust guidelines; if significantly unwell (Acute Presentation see Section 12.1) give antibiotics

in line with pyelonephritis and admit. Recurrent UTIs should be referred to urologist (see Appendix D) for cystoscopy and further investigation.

- **Renal medullary carcinoma** is more likely in patients with SCD and sickle cell trait. There should be a low threshold to investigation patients with SCD and sickle cell trait who present with

haematuria, flank pain and/or a renal mass with US +/- contrast CT or MR. The prognosis is poor with <10% 2-year overall survival.

- **Membranoproliferative glomerulonephritis** is an uncommon complication of sickle nephropathy, and uncommonly diagnosed as renal biopsies are typically avoided outside of the context of a sudden, unexplained rapid deterioration in renal function. Specialist nephrology input should be sought.

As patients with SCD age, they are also vulnerable to the same comorbidities that increase the risk of CKD seen in the general population such as hypertension and diabetes. All modifiable cardiovascular risk factors should therefore by optimised by the patient's GP. Patients with SCD have lower mean blood pressure than the general population and therefore there should be a low threshold to treat a persistent rise in blood pressure above the patient's baseline. However, patients are also prone to symptomatic hypotension and therefore antihypertensive treatment must be highly individualised in this patient group.

Recommendations

- All patients with SCD should be encouraged to have a minimum fluid intake of at least 3 L/day.
- Annual monitoring of urine protein:creatinine ratio (UPCR) and more frequently if UPCR is rising.
    - Commence ACE inhibitor when UPCR >50 mg/mmol and increase as tolerated to control.
    - If UPCR >100 mg/mmol and / or there is any derangement of renal function, refer to nephrology.
- Patients with SCD who develop acute renal failure should have close monitoring of their renal function. These patients should have adequate hydration and fluid balance; nephrotoxic drugs should be avoided.
    - SCD patients with acute kidney injury (AKI), 1.5x rise in creatinine from baseline or oliguria (<0.5ml/kg/hour for >6 hours), should follow the local AKI pathway,
    - A sudden or refractory deterioration in renal function for which there is no clear cause should be managed with early involvement of the Renal Team (see **Appendix 2 and / or 4**). Initial non-invasive investigations should include:
        - Thorough medication review
        - Urine dip and urine protein creatinine ratio
        - Capillary blood glucose
        - Bladder scan to rule out urinary retention
        - Blood pressure
        - Complement C3/C4
        - Serum protein electrophoresis and serum free light chains
        - Immunoglobulins IgG, IgA, IgM
        - Complement C3/C4
        - ANA/ANCA
        - Anti-GBM antibody
        - HIV/HBV/HCV serology
        - Renal ultrasound
- NSAIDs should be avoided in patients with stage 3-5 CKD not on renal replacement therapy (eGFR <60 ml/min)
- Consider therapeutic drug monitoring in renally cleared medications with a narrow therapeutic index.
- Patients with hypertension and ACR <3.5 mg/mmol (or UPCR < 20 mg/mmol) should be treated with a BP target of <140/90 mmHg. Patients with hypertension and ACR >3.5 g/mmol (or UPCR > 20 mg/mmol) should be treated with a target of <130/80 mmHg. An ACE inhibitor would be the drug of first choice in either instance; an ARB can be used second line.
- New-onset haematuria should be investigated, regardless of age, to exclude malignancy. Isolated microscopic haematuria in the absence of proteinuria should also be investigated.
- All patients should routine cardiovascular risk assessment and optimisation, to include blood pressure, blood glucose, lipids, smoking, BMI at a minimum.

Sexual Health / Obstetrics / Gynaecology / Urology / Fertility

Obstetric and Gynaecological

Contraception

A full range of contraceptive choices can be offered to women with SCD via their GP.

Termination of Pregnancy

Terminations should take place in a setting where there is appropriate haematology cover.

Fertility

Women with SCD usually have normal fertility, a patient reporting difficulty with fertility should be encouraged to see their GP and undergo testing and referral via normal routes.

Pregnancy

Discussion of pregnancy and conception should be embedded into routine care for women with SCD ensuring that partner has been screened for inherited red cell disorders with the couple being aware of the risks. Most maternal and fetal complications of pregnancy are more common in women with SCD (especially HbSS) and in addition they often experience an increase in frequency and / or severity of painful crisis. They are also more prone to infection, such as urinary tract infections and to thrombo-embolic problems, so pregnant women require close monitoring throughout pregnancy and prompt treatment of complications. The following is a summary of guidance and points to consider:

- All patients with a SCD must be cared for jointly by the red cell and obstetric teams with senior input and regular discussion at SHT MDT (see **Appendix 4 and 14**).
- Four weekly red cell out patient appointments during pregnancy are usual, more frequently after 28 weeks but this will depend on local hospital arrangements as some services offer joint obstetric / red cell clinics and some do not.
- **All other antenatal care** should continue in line with local policy and national guidance.
- **Communication is key** and all services should have access to the MDT records outlining treatment plans and any concerns / complications.
- For patients who are on / have been on regular blood transfusion and are iron loaded **chelation therapy must be stopped**; ideally deferiprone and / or deferasirox should be stopped prior to conception.
- **Hydroxycarbamide therapy** should be stopped 3 months before planned conception, or immediately pregnancy identified (unless the risks of stopping outways the risk of continuing).
- **Routine prophylaxis** with penicillin V 250 mg po bd, or erythromycin if penicillin allergic, is encouraged.
- **ACE inhibitors** should be stopped if it is safe to do so.
- **Hb and ferritin** should be monitored, with baseline / targets clear and patient specific.
- **Folic acid** a higher dose (5mg daily) is recommended.
- To reduce the risk of pre-eclampsia low dose aspirin (75mg daily) is recommended.
- There is an **increased risk of thrombosis** (particularly HbSC) and thromboprophylaxis with LMWH should be considered from 28 weeks gestation and all patients treated as high risk following delivery (LMWH for 10 days). An individual assessment and plan should be agreed via an SHT MDT on any patient with previous thrombotic episodes or additional VTE risk factors.
- **Method and timing of delivery:** the risk will vary from patient to patient and may change during the course of the pregnancy, however it is important to discuss and consider the risks of proceeding to term.
- **Blood transfusion in pregnancy**: the pros and cons should be considered on a case-to-case basis taking into account the patients personal choice. While blood transfusions have been shown to reduce incidence of painful vaso-occlusive crises. Indications for prophylactic transfusion may include:
    - Continuation of pre existing regimen.
    - History of SCD related complications or complications in previous pregnancy.
    - Women previously on hydroxycarbamide.
    - Hb regularly less than 75 g/l with evidence of foetal intrauterine growth retardation.
    - Twin / multiple pregnancies.

A target of Hb 100 g/l and an HbS% of approximately 50% post transfusion should be aimed for (see section on Blood Transfusion for more information). Ensure that the blood transfusion laboratory is aware that the patient is pregnant, particularly if the patient is on a regular program, so that CMV Negative units can be sourced in addition to the other requirements.

Admission during pregnancy

Follow guidance on '**Acute Presentation'**

- It is important that the obstetric team inform the red cell team (**Appendix 2**) so the patient can be reviewed promptly and cared for jointly.
- Consider prophylactic tinzaparin 4,500 units daily unless this is contra-indicated.
- Consider blood transfusion.
- Any decision regarding delivery should be made on the usual obstetric or foetal grounds**. If at all possible delivery should be postponed until after a crisis is resolved.**

Delivery

- The plan to cover delivery agreed between the red cell team and the obstetric team should be available in the patients records..
- Dehydration can precipitate a crisis so **i.v. infusion** should be sited and fluids (eg 0.9% sodium chloride or an alternative crystalloid solution) given at a rate of 3-4 litres/24 hrs continuously from the time of arrival until 24 hrs after delivery.
- Epidural analgesia can be used.
- Consider **antibiotics**, especially if febrile, in the immediate post-partum period, continuing for 5 days for example co-amoxiclav.

Post-partum

Sickling can give rise to clinical problems and patients should be monitored for critical warning signs (see Acute Presentation) for at least 48 hours post partum especially if delivery was by caesarean section.

Male fertility

Male SCD patients can have reduced sperm counts and reduced sperm mobility, particularly if episodes of priapism. Advice and referral to fertility clinic should be via the patient's GP. Discussion about family planning and conception should be embedded into routine care. Partners should be screened for inherited red cell disorders with the couple being made aware of any risks.

Urology

(Ischaemic) Priapism

Priapism is a persistent, painful erection and is generally under-reported by patients. Priapism may be ischaemic or non-ischaemic ("high flow"). SCD is typically associated with the ischaemic subtype, which arises due to a combination of mechanical occlusion of small vessels in the corpus cavernosum by deformed red cells and an imbalance in molecular mediators of vasodilatation (nitric oxide, NO, cyclic guanosine monophosphate, phosphodiesterase type 5, PDE5). Major priapism (lasting ≥6 hours) is a urological emergency associated with life-changing consequences if not managed in a timely fashion. The risk of erectile dysfunction is up to 90% in episodes lasting > 24 hours.

Priapism may also be stuttering (recurrent ischaemic priapism, RIP), lasting several minutes up to 3 hours and is often recurrent. RIP may herald major priapism and is independently associated with a risk of ED. **The identification and appropriate secondary prevention is paramount to avoid permanent sequelae; all at-risk patients should be asked about RIP during their annual review.**

It should be recognised that SCD is a risk factor for priapism, but may not be the only contributing factor. A full history should be taken to identify additional modifiable risk factors, particularly in refractory cases

(e.g. medications such as vasoactive and α-adrenergic receptor antagonists, recreational drugs such as alcohol, cannabis and cocaine, hypogonadism, anxiety disorders).

Diagnosis

In the acute setting, diagnosis is based history, clinical examination (ischaemic priapism is typically associated with painful engorgement of the corpus cavernosum with sparing of other structures such as the glans), laboratory testing (cavernous blood gas performed during aspiration demonstrating acidosis and hypoxia) and doppler ultrasonography (reduced cavernous blood flow). The diagnosis of RIP is typically based on clinical history and examination (reduced penile length and fibrosis).

Management of major priapism

Major priapism is a form of compartment syndrome and a medical emergency which requires immediate assessment and treatment at an experienced urology centre.

Front line treatment is cavernous aspiration and irrigation with saline; this may need to be repeated frequently until detumescence is achieved and blood gas no longer demonstrates acidosis or hypoxia. A shaft block is performed beforehand to achieve adequate anaesthesia. All patients also receive instillation of phenylephrine as part of front line therapy, as this improves the likelihood of successful resolution from 30% with aspiration/irrigation alone, to up to 80%.

Second line treatment with surgical penile shunt formation (fasciotomy through tunica albuginea) or surgical decompression should be offered if front line therapy fails to achieve resolution within 1-2 hours (see **Appendix 4**).

Third line treatment with penile prosthesis is offered if the above measures fail to demonstrate resolution within 48-72 hours, or if the risk of ED is felt to be high at time of presentation (i.e. if the symptoms have been ongoing for >48-72 hours at presentation). Prosthesis is performed electively within 6 weeks of initial presentation.

Hydration and rapid, adequate pain control (as per the patient's protocol) is paramount in patients who present with major priapism.

Management of RIP

Symptomatic relief may be achieved by simple manoeuvres including exercise such as jogging (which creates a steal syndrome effect to reduce penile blood flow and facilitate detumescence), neurogenic manouevers (emptying the bladder, ejaculation), hydration, oral analgesia and warm/cold compresses.

Patients with frequent RIP may be taught to self-inject phenylephrine to facilitate resolution of episodes lasting 1-2 hours at home.

Patients with recurrent episodes may be offered medication to redress the vasogenic imbalance by increasing NO availability or reducing PDE5. Ephedrine 15-30mg OD nocte (unlicensed for this indication) or Etilefrine 25-50mg OD nocte (unlicensed) may be given and often results in a marked reduction in episodes. At home patients take a dose before bed-time and a second dose in the early hours of the morning if episodes are still happening after a single, pre-sleep dose.

Anti-androgen medications (e.g. bicalutamide) may be offered to refractory patients, however undesirable side effects (e.g. reduced libido, gynaecomastia) may reduce adherence to these medications.

All patients should be offered hydroxyurea (HU), with a view to reducing the risk of priapism by better SCD control. In addition, HU has been postulated to increase NO availability thereby directly reducing the risk of priapism.

There is no robust evidence to support red cell transfusion (exchange or top up) for the management of priapism in the acute or non acute setting. However, if a patient is scheduled to undergo a surgical procedure, red cell exchange may be performed to reduce risk of acute chest syndrome associated with general anaesthetic; the haematology team should be contacted to advise on this prior to surgery.

Treatments

Blood transfusion

This section addresses blood transfusion issues specifically related to SCD. Please refer to the Trust's Blood Transfusion Policy for general principles, haemovigilance and processes. This section discusses the use of donor red cells. SCD patients will occasionally require other blood component support (platelets, fresh frozen plasma, immunoglobulins, albumin etc) treatment with these components should be discussed and agreed with the red cell team but will be in line with national and local guidance for use of these components. **In unwell SCD patients, early discussion with the haematology team and consideration of blood transfusion is paramount. Do not delay this while awaiting investigations or if the diagnosis is unclear.**
There are 2 main purposes for blood transfusion in SCD:

- Improve the oxygen-carrying capacity by correcting anaemia for which a traditional top up red cell transfusion is used.
- Reduce the percentage of circulating 'sickle cells' (HbS) by replacing them with donor non sickle (HbA) red cells.

General principles of transfusion in SCD patients:

- The guidance in the local Blood Transfusion Policy must be adhered to.
- It is essential that the requesting procedure clearly **identifies the patient as having a SCD** as these patients receive phenotyped units matched for ABO, Rh and K, sickle (HbS) negative as well as matched for any alloantibodies (or crossmatch compatible).
- All SCD patients have a full red cell phenotype or genotype at first presentation (usually within the paediatric services), records of this are held locally on the Laboratory Information Management System (LIMS), and centrally via NHS Blood and Transplant or on the NHR. If the patient is new to the hospital the information can be obtained from NHS Blood and Transplant or the NHR, if the patient is new and there are no records additional samples will be required but it is essential that a good history of previous blood transfusions is obtained. If the patient has received donor blood within the last 4 months samples will need to be referred for genotyping as phenotyping could give false positive results due to circulating donor red cells.
- If blood is required urgently CALL the blood transfusion laboratory and discuss with senior laboratory staff. **In acutely unwell or bleeding patients, the 'rules' might need to be reconsidered**. If life-saving, timing is more important than perfectly matched, age, volume, HbS negative or even antigen negative units. This decision should be discussed with senior member of the red cell team and Hospital Transfusion Team and / or NHS Blood and Transplant (see **Appendix 4**).
- For cardiovascular stable patients requiring top up transfusions, do not exceed the maximum infusion rate of 5 mL/kg/hr.
- Exchange transfusions can be carried out using apheresis machines (ARCE) or by a manual techniques. ARCE has the advantage that it is more effective in lowering the percentage of HbS quickly once started however the disadvantage is that good venous access is required (inlet and outlet) and that large quantities of donor red cell units are required. For ongoing treatment ARCE is the treatment of choice as the interval between transfusions tends to be greater and there is usually a reduction in iron loading. The advantage of a manual exchange is that it can be started with one venous access and with one or two units of blood being available. For acutely ill patients requiring exchange start with a 'top up' if Hb <80 g/L; manual exchange while units are being sourced, got ready and venous access is being sorted. There should be sufficient medical staff trained in the manual procedure should this be required.
- For patients that require transfer for ARCE consideration should be given to providing a top up transfusion or small volume exchange prior to transfer.

- No unscheduled ARCE should be initiated without consultation with the Consultant Haematologist on call.
- Hospitals have different arrangements for accessing automated red cell exchange services, all staff should be aware of the pathway both in and out of normal working hours (see **Appendix 2** for contact details which has ARCE contact details both in and outside of normal working hours).

Indications for Blood Transfusion

The main indications for transfusion are summarised below:

- **Top up red cell transfusion:** Aim to raise Hb to no higher than baseline Hb.
  - Symptomatic / acute anaemia (for example sequestration, aplastic crisis).
  - Possible indication: Can be used in incipient chest syndrome if there is sufficient "space" i.e. a top up to raise the Hb to no higher than 110g/L
- **Emergency red cell exchange (manual or ARCE)**: Aim to reduce the percentage of sickle (Hb S) to less than 30% with a post exchange Hb of approximately 100 g/L and a HCT of approximately 30%, while maintaining a steady blood volume.
  - Acute stroke
  - ACS
  - Severe sepsis
  - Acute hepatic sequestration
  - Acute multiorgan failure
  - Progressive intrahepatic cholestasis
  - Other life threatening complications
  - Possible indication: Persistent priapism despite medical therapy
- **Long term red cell exchange programme**
  - Primary and secondary stroke prevention
  - Possible indications include: Repeated severe painful crises or acute chest syndrome with no or poor response to hydroxycarbamide, pulmonary hypertension, progressive organ compromise (ie progressive renal failure).
- **Short term or one off red cell exchange**
  - Elective surgery (each case should be discussed at SHT MDT **Appendix 14**)
  - Possible indication: Pregnancy, leg ulcers.

Please note that the following are **NOT indications for transfusion**:

- Asymptomatic anaemia, especially if there is plentiful polychromasia, and a good reticulocyte response. Transfusion is not usually necessary unless Hb < 50g/l, depending on age and clinical state of patient.
- Uncomplicated painful episode. Transfusion does not reduce the pain or duration of opioid treatment.
- Uncomplicated pregnancy, especially if mild sickle cell

phenotype. Considerations / contra-indications include:

- History of delayed haemolytic transfusion reaction or hyperhaemolysis
- Multiple allo-antibodies
- Rare blood group phenotype (eg U-negative)

Manual Exchange Blood Transfusion Summary on process

In acutely ill patients where clinical decision by red cell team is that a transfusion is required it is important to **start as soon as possible;** depending on the patients starting Hb this could be a top up transfusion and / or starting a manual exchange while ARCE is organised. *It is not appropriate to delay the start of treatment while waiting for ARCE.* The aim would be to **start** blood transfusion within **one hour** of the decision.

- Calculate the approximate number of units required for an exchange, depending on starting haemoglobin and the patients EBV (for adults = weight x 70), as a rough guide for a 70kg patient order:
  - 8+ units if Hb >80g/l
  - 6-8 units if Hb 60 to 79 g/l

- 4-6 units if Hb <60 g/l
- Ensure adequate venous access, pink or larger cannula, if not able to obtain venous access.
- If patient is acutely unwell inform critical care that a manual exchange is to be performed as an emergency and that the patient may deteriorate.
- Discuss urgent samples with laboratory, ensure blood transfusion laboratory has a valid request for exchange and agree a time that units will be ready.
- Under all circumstances **the local Blood Transfusion Policy must be followed**.
- There is a manual RCE tutorial available via the NHS Blood and Transplant website.

Equipment Required

- Gloves
- Assorted venflons
- An assortment of syringes from 5 ml – 50 ml
- Venesection packs
- Three-way tap
- Saline flushes
- Sodium chloride 0.9% and appropriate administration set.
- Blood pressure monitor
- Saturation monitor
- Adult/paediatric cardiac arrest trolley readily accessible.
- Observation chart, blood prescription chart and fluid balance charts (in line with local policy)
- Sharps Bin

Monitoring

Observations in line with local blood transfusion protocols BUT it is important to be mindful to observe patient while venesection is in process and to ensure crashing blood pressure and / or increased heart rate are responded to.

Simplified Protocol for Emergency Manual Exchange

This protocol is easier to work with than a weight-based protocol and is useful in an emergency particularly for those who do not perform the treatment routinely:

- Ensure patent venous access with three way tap.
- Infuse 500ml to 1L of normal saline over approximately 30 minutes to ensure pre hydration.
- Do appropriate checks on first red cell unit and attach to ensure unit can begin should the patient have a hypotensive emergency.
- Venesection, depending on the access, can be by attachment of a venesection bag (one unit, 450 to 500ml, either by weight or by eye using the volume marks on the pack) or by aspiration using a large volume syringes discarded into a sharps bin. **Note: slow venesection is important if significant renal or cardiac abnormalities or if cardiovascularly unstable.**
- Consider fluid balance using additional saline to make the red cells up to 450 ml. Most donor red cell units in the UK are between 220 to 320 ml made from 500ml of donor whole blood with a haematocrit (Hct) 0.5 to 0.7 so if a 'like for like' exchange is used the patient's final Hb and Hct will be too high. Consider fluid balance using additional saline to make the red cells up to 450ml.
- Consider blood warmer in large volume exchange in line with local blood transfusion policy where donor red cell units are to be transfused quickly or greater than four units will be transfused.

Hb > 80 g/l 2 units are removed before infusion of red cells resulting in a more efficient lower of the patient's HbS%.	Venesect 1st unit	WHILST	Replacing with 500 mls of normal saline
	Venesect 2nd unit	THEN	Transfuse 1st unit over 30-40 minutes. *
	Venesect 3rd unit	THEN	Transfuse 2nd unit over 1 hour
	Venesect 4th unit	THEN	Transfuse 3rd unit over 2 hours

However this is not suitable if the patient is cardiovascularly unstable and / or becomes hypotensive when the first unit should be started sooner.	Check FBC and HbS%	If Hb<90g/l:	Transfuse 4th and consider 5th units (over 3 hours each)
		If Hb>90g/l:	Restart from "venesect 1st unit" if HbS% unsatisfactory
Check Hb and HbS% **Aim:** Hb 100 g/L and HbS less than 30% if not achieved venesect and transfuse one unit and re check Hb / HbS%			
Hb 60 – 79g/l	Venesect 1st unit	THEN	Transfuse 1st unit over 30-40 minutes. *
	Venesect 2nd unit	THEN	Transfuse 2nd unit over 1 hour Transfuse 3rd unit over 2 hours Transfuse 4th unit over 2-3 hours
	Check FBC and HbS	If Hb<90g/l:	Transfuse 5th and consider 6th units (over 3 hours each)
		If Hb>90g/l:	If HbS% or clinical improvement unsatisfactory, follow 'venesect 1st unit' for Hb > 80 g/l
Check Hb and HbS% **Aim:** Hb 100 g/L and HbS less than 30% if not achieved venesect and transfuse one unit and re check Hb / HbS%			
Hb < 60 g/l	Transfuse 1st unit over approximately one hour.		
	Transfuse 2nd unit over 1-2 hours		
	Check FBC and HbS	If Hb<80g/l:	Transfuse 3rd unit
		If Hb>80g/l:	Follow 'venesect 1st unit' for Hb > 80 g/l

- A repeat Hb is required on completion of the procedure and **should not exceed 100 g/L if Hb S % more than 30%. Haematocrit should not exceed 0.33.** If this is the case, consider further venesection.
- An exchange of >1/3 of the blood volume (3 units in an average 70Kg) manually exchange without a rest period risks thrombocytopenia and hypocalcaemia, check bone profile and FBC.
- Protocol needs to be adapted for patients who have been transfused in the last three months as starting who may start with a lower HbS percentage.
- **Weight based protocols** should be considered for patients who are acutely unstable to achieve a better balance taking account of the patients starting Hb and the volume of red cells / saline infused, for example:
  - **Hb <70 g/l:** top up transfusion to achieve Hb of approximately 80 g/l then total volume 20 ml / kg out, 15ml / kg red cells + 5ml / Kg saline in, repeat (adjust if necessary) until HbS < 30% and Hb 80 to 100 g/l.
  - **Consider ARCE as soon as possible** (see below).

Automated Red Cell Exchange Blood Transfusion

Below is supplied to give guidance on arranging a ARCE and does not address the actual operation as this can only be performed by trained authorised staff. Individual hospitals will have access to apheresis services off site or on-site services provided by outsourced providers. Please refer to **Appendix 2 and 4** for contact details.

- **Venous access:**
  - The patient will need two points of venous access (inlet and outlet). This can be achieved by the placement of two peripheral cannulas, or by a double lumen central venous catheter. NOTE: a PICC line is not suitable for the apheresis machine. Other (long-term) options are an A/V fistula or Dual-Lumen Port-a-Cath.

- Refer to the Trust's policy on obtaining venous access (**Appendix 2**).
- Stimulate patient to drink well before the procedure to prevent vasovagal collapse and help improve venous access.

Ordering blood:

- In an emergency ask the laboratory to obtain and get ready 10 units (for patient's <70Kg) and 12 units (for patient's >70Kg).
- If planned regular exchange there will be a patient record on previous procedures outlining the number of units used per procedure and the length of time between procedures.
- The machine can run two programmes for the purpose of red cell apheresis:

- Red Cell Exchange; an iso-volaemic exchange of red blood cells.
- Depletion / Exchange cycle; starts with an iso-volaemic haemodilution by replacing patient red cells with a saline solution, followed by the red cell exchange.
  The benefits of depletion is that fewer donor units are used to achieve the post exchange of a HbS of less than 30 percent, in addition it is ideal in patients who have iron overload. The drawback is that not all patients tolerate the depletion cycle. If the patient requires an emergency exchange and they are unstable it is better to use an iso-volaemic straight forward exchange.

- The pre transfusion and target parameters are programmed into the machine prior to running the cycle. The following are required:
  - Patient consent for procedure and blood transfusion (in line with local policy).
  - A recent height and weight.
  - FBC (Hb, MCV, Hct), HbS% (or estimation of ie 90% in untransfused or estimated if transfused in last eight weeks).
  - Biochemistry in particular calcium and magnesium with supplementation if low.
- Withhold therapeutic anticoagulants if a central venous catheter is to be inserted. Anticoagulation can be continued for connecting to a porth a cath or for insertion of peripheral cannulas; for midlines discuss with Consultant Haematologist.
- Consider withholding ACE inhibitors to prevent vasovagal collapse.
- Following the ARCE it is important to repeat FBC, HbS%, U+E and Bone profile to review results to ensure Hb approximately 100 g/l, HbS below 30% and that the K+ and Ca are within the normal ranges with any deficiencies replenished.

Specific complications with ARCE

- Citrate related hypocalcaemia: tingling sensation, nausea and vomiting, hypotension.
  - Prophylactic oral /IV Calcium given to all patients with a (borderline) low calcium prior to starting the ARCE.
    - Reduce the speed of the procedure.
    - Ensure calcium is available to give to a patient complaining of above symptoms.
- Anxiety, fatigue and boredom are common and it is essential that the patient feels supported, is monitored closely and receives assurance.
- Apheresis induced thrombocytopenia is a rare complication unless the patient's pre procedure platelet count is low. If the patient's platelet count is less than 100 prior to procedure refer to a senior member of the red cell team.

Complications related to blood transfusion

The complications related to the transfusion of red blood cells are the same as for any patient receiving donor blood. **The management and reporting of blood transfusion adverse events and complications is covered under the local Blood Transfusion Policy.**

Hyperhaemolysis / Delayed Haemolytic Transfusion Reaction

Hyperhaemolysis / delayed haemolytic transfusion reaction is a well-recognised but rare complication of blood transfusion in patients with SCD. It is characterised by rapid haemolysis following a blood transfusion, with the post-transfusion haemoglobin (Hb) often lower than the pre-transfusion Hb. Often the patient's red cells as well as the donor red cells are destroyed. It may be associated with a fever and with pain typical to SCD patient's a painful crisis. Sometimes a new red cell allo antibody is formed and sometimes there is no evidence of allo antibody formation. The direct antiglobulin test (DAT) can be

positive or negative. Sometimes there is a marked reticulocytopenia. **Additional transfusion has been associated with increasing haemolysis and worsening anaemia and should be avoided if possible**. Advice and guidance should be sought urgently from HCC team and NHS Blood and Transplant (Appendix D). Treatment is with intravenous immunoglobulins (IVIg) and IV methylprednisolone. Other agents such as **Eculizumab and Rituximab** may be necessary but should only be used after senior MDT agreement. Erythropoetin, iron, B12 and folate replacement should also be considered. Hyperhaemolysis can recur and it is essential that the patients sPCP, and the blood transfusion laboratory record, is updated so the patient is not accidentally transfused without prior treatment with IVIg and IV methylprednisolone. Episodes of hyperhaemolysis are reportable nationally, via the hospital transfusion team, and on the NHR via the red cell data management team (see Appendix 2).

Diagnosis:

Hyperhaemolysis / delayed haemolytic transfusion reaction should be considered in any patient with SCD who presents with increasing haemolysis after receiving blood, typically 7 to 14 days post transfusion. Clinical features include increasing jaundice, dark urine ('coca-cola' coloured), anaemia, fever, back, leg or abdominal pain, hepatomegaly or hepatic discomfort, often associated with severe bone pain, typical of sickle crisis.

Investigations:

- FBC: increasing anaemia.
- Full biochemistry and marker for haemolysis: raised unconjugated bilirubin, raised LDH.
- Reticulocytes: may be raised (in keeping with haemolysis) or decreased due to suppressed red cell production.
- Direct Antiglobulin Test (DAT): may be positive or negative.
- Group and Antibody Screen: Hyperhaemolysis often occurs without evidence of new red cell allo-antibody formation but regular group and screens should be performed as red cell allo-antibodies may become apparent up to 3-4 months after the haemolytic episode.
- Haemoglobin electrophoresis: A rapid increase in HbS% indicates haemolysis of the transfused blood; urine haemoglobin electrophoresis is also useful.
- Ferritin, folate and B12 levels: This may aid in decisions about replacement.
- Differential diagnosis is a delayed haemolytic transfusion reaction due to new allo-antibodies and blood must be sent to the transfusion laboratory for the investigation of new allo-antibodies.

Treatment:

- Discuss all suspected cases should be urgently via the HCC MDT.
- Prescribe Folic acid 5mg.
- Primary treatment is with immunosuppression: IV Methylprednisolone and IVIg
- Consider treatment with erythropoietin and IV iron and / or B12.
- If further transfusion necessary consideration could be given to obtaining genotypically matched / or best matched units but this will be following discussion with the NHS Blood and Transplant team.
- The patient's Hb and haemolysis parameters must be checked regularly after an episode and / or treatment, for at least 3 weeks. However in patient's with Hb <50g/l this needs to be balanced with blood being lost in sampling; paediatric sample bottles can be considered.
- **Intravenous immunoglobulin (IVIg):** Use 1g/kg for brisk haemolysis but consider lower doses (0.5g/kg) for pre-treatment. Up to 1g/kg once daily for 2 days (total dose = 2g/kg). Administration and choice of preparation as per Trust guidance.
- **Methylprednisolone** in adults: 500mg IV for 2 days. Review dose after 2 days. Consider continuing prednisolone 30 mg OD per os for 5-7 days + taper over 3 days, especially if previous evidence of late onset hyperhaemolysis.
- **Erythropoietin** NeoRecormon® 300units/kg subcutaneously once daily for 5 days, followed by 300units/kg once daily on alternate days (i.e. 3 times per week)
- **Eculizumab and Rituximab** have been used in the treatment of hyperhaemolysis and DHTR. Second line treatment with eculizumab should be considered for patients when the rate of rapid haemolysis with symptomatic anaemia or compromise of organs (respiratory failure, renal failure,

neurological symptoms) continues despite first line treatment with IVIg and steroids. Rituximab can be considered in adults when all the criteria for giving eculizumab have been met AND there

is a need for ongoing transfusion therapy. Dose: Eculizumab 900mg iv with a second dose 7 days if there is evidence of efficacy but ongoing haemolysis. Rituximab two doses of 375 mg / m^2 given 7 to 14 days apart for prevention and up to a maximum of four doses given 7 days apart for management.

Crizanlizumab

Crizanlizumab is a P-selectin inhibitor which initially demonstrated a reduction in the annual rate of VOCs in the phase 2 SUSTAIN study and was granted a conditional licence in England. However, the confirmatory phase 3 STAND study failed to demonstrate a statistically significant benefit and the MHRA licence and NICE reimbursement was subsequently withdrawn in early 2024.

Hydroxycarbamide

Hydroxycarbamide (also known as hydroxyurea) is licensed in the UK for the prevention of recurrent painful crisis in patients with SCD. It is an inhibitor of ribonucleotide reductase and has been used as an oral anti-proliferative drug for several decades. Studies have shown that treatment with hydroxycarbamide can decrease episodes of pain, reduce the need for transfusion, reduce the risk of chronic and acute complications and improvement in patient survival. Its mode of action in SCD is based on its ability to increase HbF levels and to reduce intercellular adhesion, improving blood flow and reducing vaso- occlusion. Further information and a patient information leaflet is provided in **Appendix 9**.

In addition to the increase in HbF%:

- raised haemoglobin concentration (Hb) levels
- increased mean cell volume (MCV)
- reduction in absolute reticulocyte count (ARC)
- reduction in WBC count
- and / or reduction in platelet count

have been seen.

Concerns:

Despite the clear benefits of hydroxycarbamide, it remains under-utilized within the adult population partly due to concerns about reported side effects and the need for regular blood monitoring. Side effects include fatigue, GI symptoms, darkening of skin and nails, hair thinning and marrow suppression. The drugs effect on fertility in men is unclear however there is good evidence that fertility returns to baseline after stopping hydroxycarbamide for 3 months.

Recommendations:

- All patients with **HbSS and HbSb^0** should be offered treatment with hydroxycarbamide. A strong recommendation should be made to any HbSS and HbSb^0 patient who has three or more moderate / severe sickle crisis in a twelve month period or have had severe or recurrent ACS. On-going discussion about starting treatment or the effectiveness of the regime should be part of the comprehensive annual review.
- Full informed written consent should be obtained and documented in line with local practice.
- Hydroxycarbamide therapy should be considered in adults and children with SCD with **genotypes other than HbSS and HbSb^0 on a case-by-case basis** particularly if they experience three or more moderate to severe pain crisis annually.
- In adults with a previous history of acute ischaemic stroke or infarcts, hydroxycarbamide should be **recommended** as second line therapy for **secondary stroke prevention** when transfusions are contraindicated or unavailable.
- The potential benefits of hydroxycarbamide in **preventing end organ damage** (renal/splenic and retinopathy) should be **discussed** with all patients with HbSS and HbSb^0.
- Baseline elevation of HbF should not affect the decision to initiate hydroxycarbamide therapy (except for in HbS/Hereditary Persistence of Foetal Haemoglobin)

- Patients should be made aware that it may take several months to achieve an optimal rise in HbF.

- Hydroxycarbamide should be avoided / stopped if eGFR < 30 ml/min/1.73 m2.

Other treatment-related recommendations:

- Should a male patient wish to be considered for semen analysis and cryopreservation refer to Appendix 4 for local arrangements.
- Contraception is advised for patients on hydroxycarbamide.
- Consider stopping hydroxycarbamide pre-conception in male and female patients and in pregnant women if the patient is not at high risk of serious complications relating to sickle cell disease. Typically a 3 month pre-conception washout is advised.
- Prenatally and during pregnancy, consider a transfusion programme if there is a severe clinical phenotype as an alternative to hydroxycarbamide treatment.

Dosing

Patients with the highest HbF% are more likely to benefit therefore the main aim is to optimise HbF% without causing excess bone marrow suppression. Therefore, patients should be titrated to their maximum tolerated dose (MTD).

- In adults start at 15 mg/kg/day (rounded up to the nearest 500 mg). 5–10 mg/ kg/day if the patient has chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 ml/ min/1.73 m2).
- Increase dose by 5 mg/kg every 8–12 weeks, aiming for a neutrophil count of 2–3 x 10^9/l. Up to a maximum dose of 35 mg/kg/day. Stop medication and if **neutrophils fall below 1 x 10^9/l or if there is other haematological toxicity**.

Monitoring

- Hydroxycarbamide therapy should be continued during hospitalisations or illness **unless febrile neutropenia or bleeding with thrombocytopenia**.
- Avoid use with didanosine, stavudine and clozapine.
- Caution with yellow fever vaccine (although risks and benefits should be considered).
- Review treatment if cutaneous vasculitic ulcerations develop.
- Patients should be informed to present to hospital if unwell with high fevers and infection and inform hospital staff to perform a FBC in case of neutropenia.
- There must be local arrangements for on-going monitoring of patients on hydroxycarbamide. Often virtual nurse lead clinics are appropriate to review blood tests and arrange repeat prescriptions on stable patients.
- Initially / or following dose change patients should attend for blood tests (FBC, Retic, renal and hepatic function and HbF%) ever 2 weeks. Once dose stable bloods can be checked every 8 to 12 weeks. Target range:
    - **Neutrophils** 2 – 3 x 10^9/l (> 1 x 10^9/l continue on current dose < 1 x 10^9/l stop and recheck weekly until > 1 x 10^9/l then restart at lower dose)
    - **Platelets** > 100 x 10^9/l (>80 x 10^9/l continue on current dose, recheck in one week; < 80 x 10^9/l stop and recheck in one week; < 80 x 10^9/l
    - **Reticulocytes** > 80 x 10^9/l
    - Renal increase in **serum creatinine** >50% from baseline stop and monitor until recovered, restart on lower dose.
    - Hepatic increase in **ALT** > 100% from baseline stop and monitor until recovered, restart on lower dose.

Iron Chelation

While blood transfusion in SCD can be life saving there is a risk of iron toxicity in patient's who have received top up transfusions over their life time. There is approximately 200 mg of iron in every red cell unit transfused and in some patient's transfusion can lead to excessive iron stores. Blood transfusion in SCD patients has been shown to lead mainly to iron deposition within the liver. With the gold standard for transfusion in SCD patients being ARCE the number of patients requiring therapy for iron loading should reduce; however it is essential during the patient's comprehensive annual review that time is

taken to consider the number of units transfused and the modality of the transfusion (top up or exchange ie positive,

negative or neutral iron loading) both over the last preceding 12 months and the lifetime total. There is less robust evidence regarding iron chelation in SCD but the aim is to reduce the risk of complications due to iron overload ideally to maintaining an average serum ferritin below 1000 ng/ml and liver iron below 5 mg/g dry weight. As top up transfusions give the largest iron burden other inherited red cell disorder patients, such as those with beta thalassaemia major, require iron chelation from the first years of life so detailed guidance and further information can be found within the Thalassaemia guideline (UKTS, 2024). **Individual Chelators**

There are three licensed chelator drugs, desferrioxamine ['Desferal', DFO] given subcutaneously over 12 hours, deferiprone ['Ferriprox', DFP] oral typically three times a day, and deferasirox ['Exjade', DFX] orally once a day. Desferrioxamine is still considered to be the first line treatment with deferasirox considered if desferrioxamine is not tolerated or inadequate. Detailed information on doses and monitoring is available in the Thalassaemia guideline (UKTS, 2024), NHSE recommendations on iron chelation (NHSE, 2022) and BSH guideline (Shah, 2021). **Dosing and monitoring should be in line with local pharmacy guidance as outlined in BNF.**

Patients receiving / received intermittent or occasional top up transfusions

- These patients can accumulate considerable amounts of iron over one year.
- Ferritin should be assessed regularly, at least at annual review
- Liver MRI (R2) monitoring undertaken if the ferritin is persistently >1000µg/l. Note: Ferritin is an acute phase protein and is often raised in patients with SCD. Results should be correlated with the clinical status of the patient and the CRP. Iron studies are sometimes more useful.
- Iron chelation should be offered to all patients with liver iron values above 7mg/g/dw and considered for those with liver iron concentration of 5-7mg/g/dw.

Patients on regular top up transfusion programme

- These patients should be offered iron chelation therapy once 10-20 units of blood have been administered and the ferritin is above consistently above 1000µg/l.
- Iron chelation should be continued depending on the transfusion regimen with the aim of keeping liver iron <5mg/g/dw and ferritin below 1000µg/l.

Patients on automated regular exchange transfusions

- Many patients on long-term transfusion therapy will receive automated exchange transfusions. These are less likely to cause iron loading than long term simple transfusion and are recommended by the National Institute of Health and Clinical Excellence (NICE) https://www.nice.org.uk/guidance/mtg28 .
- Some patients may still load iron, particularly if the post-exchange haemoglobin is higher than that pre-exchange. MRI scanning is indicated if there is a raised or increasing ferritin level (>1000 µg/l).
- Patients who are iron loaded (LIC >7mg/g/dw) when they embark on long-term automated transfusion therapy should be treated with iron chelation therapy and be monitored for iron overload with serial serum ferritin and MRI LIC.
- Iron chelation can be stopped once the ferritin is <500µg/l or liver iron <5mg/g/dw.
- All patients who are loading iron on the automated exchange transfusion programme should be discussed in local / SHT in MDT (**Appendix 14**) to review timings, indications and technicalities of their procedures are reviewed to see if patients may benefit from stopping transfusions, changing in frequency, other disease modifying interventions or any other options.
- Where possible patients who are iron loaded or iron neutral (and not iron deficient) should be offered hypovolaemic depletion on the apheresis machine.
- Ferritins, pre and post Hcts, S% should be reviewed three monthly at MDT meetings to ensure targets are being met and precious donor units are not being used unnecessarily.

Monitoring of Iron Overload

- **Clinical assessments** of iron loading are not helpful in routine practice: by the time there is obvious skin darkening, palpable hepatomegaly, cardiomegaly, or cardiac rhythm disturbance, iron loading is advanced and so investigations aiming to detect and enable correction of iron are required, on a regular basis, before these signs develop.
- **Serum ferritin** levels should be **monitored at least every three months**; levels maintained in the range 500-1500 µg/l over the long term carry a relatively low risk, best if around / below 1,000

ng/ml. It is recommended to include full iron studies (TIBC, Fe and transferrin saturation) from time to time.

- **Imaging Schedule**

Stable or falling ferritin <1000 µg/l	Liver MRI R2 every 2 years
Rising ferritin >1000 µg/l	Liver MRI annually
Moderate liver iron LIC >7mg/g/dw	Repeat Liver MRI (R2) annually consider T2*
Moderate to severe cardiac / liver iron, poor compliance, rising ferritin	At least annually MRI R2 and T2*

- **Patients with SCD** should be referred for a cardiology opinion if there are concerns regarding cardiorespiratory symptoms, abnormal echocardiograms and abnormal MRI scans demonstrating cardiac iron overload. They should also be referred to the endocrinology team if there are concerns regarding pituitary or hormonal disturbance which may be due to iron overload (see **Appendix 4** for referral).

New therapy / gene therapy / future opportunities

Any new therapies or treatments under consideration of the red cell team or mentioned by patients that they would like to consider / explore that are not covered in this document should be taken to local / SHT and / or HCC MDT for discussion (see **Appendix 14**).

Transplantation

Allogenic haematopoietic stem cell transplantation (allo-HSCT) is the only currently available therapy that can cure sickle cell disease.

Indications for HSCT:

The results of sibling-HSCT in adults show survival rates of 81-100%. For adults with severe SCD, including those with additional co-morbidities e.g. stroke, pulmonary hypertension, severe disease, the mortality rate is 25% over a 10-year period. Therefore, survival with HSCT is better than survival with current standard care and HSCT should be consider in patients with predicted poor outcomes, for example:

- History of greater than three admissions per year for severe pain crises or other acute complications despite supportive care measures (optimal treatment with hydroxycarbamide or transfusion therapy).
- Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide or transfusion therapy.
- Clinically significant stroke or progressive cerebral vasculopathy
- Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type/history of hyperhaemolysis, rendering it difficult to continue/commence chronic transfusion.
- Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate therapy.
- Established end organ damage relating to SCD for example vasculopathy or hepatopathy.

Standard exclusion criteria for HSCT includes active hepatitis or HIV infection, end stage liver cirrhosis or organ failure, active leg ulcers, pregnancy, failure to comply with adequate iron chelation.

Discussion regarding transplantation should be considered in outpatients, particularly for those patients meeting the above indication. HLA typing of siblings may be considered if appropriate to determine if a suitable donor may be available.

All patients that wish to be considered and / or that meet the above criteria need to be discussed at local / SHT / HCC MDT then submitted to the NHP for agreement. See Appendix 14 for MDT submission and NHP website for referral.

Voxelotor

Voxelotor has been approved by NICE for treatment of certain patients living with SCD. It is an option for treating haemolytic anaemia caused by SCD in adults who are intolerant of hydroxycarbamide or where hydroxycarbamide alone is insufficiently effective. Patients that might fulfil the criteria should be discussed at local MDT and then the case taken to HCC MDT for approval. Please refer to https://www.nice.org.uk/guidance/ta981 for criteria and information.

Sickle Cell Disorders (SCD) Guidelines Appendices

Appendix 1: Equality Impact Assessment

Equality Impact Assessment	
Does the scheme affect one of the following groups more or less favourably than another?	**If yes, explain impact and any valid legal and/or justifiable exception**
Age *Consider and detail (including the source of any evidence) across age ranges on old and younger people. This can include safeguarding, consent and child welfare.*	This document covers the care of ADULT patients. There is NO impact of age.
Disability *Consider and detail (including the source of any evidence) on attitudinal, physical, and social barriers.*	No
Sex *Consider and detail (including the source of any evidence) on men and women (potential to link to carers below)*	No (note: there are some differences within the blood transfusion requirements in line with national recommendations).
Gender reassignment (including transgender) *Consider and detail (including the source of any evidence) on transgender and transsexual people. This can include issues such as privacy of data and harassment.*	No
Marriage and civil partnership *Consider and detail (including the source of any evidence) on people with different partnerships.*	No
Pregnancy and maternity *Consider and detail (including the source of any evidence) on working arrangements, part-time working, infant caring responsibilities.*	No (note: there are some differences within the blood transfusion requirements in line with national recommendations).
Race *Consider and detail (including the source of any evidence) on difference ethnic groups, nationalities, Roma gypsies, Irish travellers, language barriers.*	No
Religion or belief *Consider and detail (including the source of any evidence) on people with different religions, beliefs or no belief.*	No
Sexual orientation *Consider and detail (including the source of any evidence) on heterosexual people as well as lesbian, gay and bi-sexual people.*	No
Carers *Consider and detail (including the source of any evidence) on part-time working, shift-patterns, general caring responsibilities.*	No impact
Is the impact of the scheme likely to be negative? If so, can this be avoided? Can we reduce the impact by taking different action?	No – it is intended to have a positive impact on SCD patients.

Appendix 2: Contact Details of Red Cell Team (amend locally)

Essential contact details of red cell team			
Local Adult Red Cell Medical lead:			
Dr Suzanne Docherty	*Suzanne.docherty@nnuh.nhs.uk*	*x2895*	*Alertive*
Local Adult Red Cell Nursing lead:			
Jo Read	*Joanne.read@nnuh.nhs.uk*	*x1778*	*Alertive*
Local Paediatric Red Cell Medical lead:			
Dr Jo Ponnampalam	*Jo.ponnampalam@nnuh.nhs.uk*	*x3622*	*Alertive*
HCC contact			
Dr Emma Drasar	*e.drasar@nhs.net*	*0203 447 9456*	

Out of normal working hours contact details	
Local Adult Red cell Team	
On call Haematology Consultant/SpR x2919/6744 or mobile via switchboard	*5pm – 8am weekdays and across weekends*
Local Paediatric Red Cell Team	
On call Paediatric team via switchboard	*5pm – 8am weekdays and across weekends*

Normal working hours contact details	
Local Adult Red cell Team	
SpR x2919 or via Alertive	*8.30am-5.30pm*
Local Paediatric Red Cell Team	
Who and how to contact	*Clarify hours*

Adult Clinical Haematology Team / Paediatric Team	
Local Clinical Haematology	
SpR x 2919	*8.30am-5.30pm Mon-Fri Weekends 8.30am-3.30pm (then via switchboard on mobile)*
Consultant x6744	*8.30-7pm Mon-Friday (variable at weekends) or 24h via switchboard on mobile*
Local Paediatric Team	
On Call Paediatric SpR	*24h - Alertive*
Pharmacy	
Reception	*5401/5402 – normal working hours On Call Pharmacist out of hours*
Acute presentation local arrangements	
Adult Patients – to contact Haematology CNS team or go straight to ED	*Paediatric Patients – to contact and attend CAU*

Other key contacts		
Venous access	*IRU x3114*	*On call Anaesthetist*
Apheresis team	*On call haematologist*	*24h – see above*
Blood Transfusion Laboratory	*In hours X2906*	*Out of hours x2906*
HDU / ICU admission	*In hours*	*Out of hours*
Escalation of patient with critical warning signs	*x4444/Alertive RRT*	*x4444/Alertive RRT*
Escalation to SHT / HCC of critically ill patient	*x4444/Alertive RRT*	*x4444/Alertive RRT*
PCA pumps	*Acute Pain Team – Alertive or online referral*	*Acute Pain Team - Alertive*
Microbiology antibiotic advice	*x4587*	*Via switchboard*
Contact details for patient to red cell team	*Adult patients call 01603 646753 Paediatric patients call 01603 289954*	

Appendix 3: Acute Management Essential Care (amend locally)

SPECIFIC COMPLICATIONS

- Sepsis
- Acute Chest Crisis
- Stroke
- Organ dysfunction
- Acute anaemia, aplastic crisis, transfusion reactions
- Priapism
- Osteomyelitis
- Abdominal crisis; girdle syndrome
- Sequestration
- May require urgent surgery

PATIENT MANAGEMENT

1. Pain relief.
2. Alert Haematology team.
3. Monitoring: pain score, O2 sat on air, temp, BP, HR, GCS and respirations arrival and every 30 minutes until pain under control then hourly or four hourly depending on analgesia and pain score.
4. Intravenous access and bloods.
5. Adjunctive treatment: hydration, antiemetic, laxatives, antipyretics, VTE prophylaxis, incitive spirometry
6. Treat specific complications: antibiotics, management of pregnancy, priapism, prepare for urgent blood transfusion.
7. Investigations:

7.a. Bloods: FBC, Retic, U&E, LFT, LDH, Bone, CRP group and antibody screen.

8. Additional investigations:

8.a. Blood cultures (temperature >38^{o}C or sepsis).
8.b. Urine dip and MSU.
8.c. COPAN if respiratory symptoms.
8.d. ABG if O2 sat low.
8.e. Parvovirus, mycoplasma if suspected.
8.f. Yesinia cultures (if on desferrioxamine with diarrhoea / fever).
8.g. Malaria screen if recent travel.
8.h. Amylase if abdominal symptoms.
8.i. CXR
8.j. ECG
8.k. Other as indicated

Appendix 4: Referrals to other specialities (amend locally)

It is essential that referrals are made to teams with knowledge and experience in the treatment of patients living with sickle cell. The table below summarises local arrangements for referral to other specialties for recognised complications of SCD. Medical complications and problems unrelated to the SCD diagnosis must be referred to the patients GP.

Problem	What to do	When to refer	Who to refer to
Abdominal / Hepatobiliary			
Symptoms suggestive of gallstones	Request ultrasound liver and biliary system	If gallstones identified, and any evidence of obstruction OR continuing symptoms, so that lap cholecystectomy would be considered.	Referral to surgeons *General Surgery on call via Alertive or switchboard*
Liver related problems	Conjugated and unconjugated bilirubin, full liver function blood tests, abdominal ultrasound. Viral hepatitis screen.	Evidence of sickle cell hepatopathy, cirrhosis, unexplained hepatomegaly	Referral to gastroenterology *Gastro SpR on call via Alertive (out of hours via H@N)*
Acute hepatitis / liver failure		Urgent discussion and transfer to specialist liver unit.	Referral to hepatologist *Gastro SpR or Consultant on call via Alertive*
Circulation / Pulmonary / Cardiac			
Acute anaemia / Hypovolemia			Discuss possible HTR with local transfusion or NHS BT Consultant *Haematology SpR x2919 or Alertive, or Consultant on call*
Cardiac problem	Symptomatic, request ECG / 24 hr tape / echocardiogram as appropriate to symptoms. IF possible transfusional iron overload arrange cardiac MRI (T2*)	Any abnormal findings on investigation which require specialist input. T2* <10ms	Refer to Cardiology *Outpatient referral to Cardiology (or on call Cardiology SpR on Alertive)* Escalate to HCC / NHP for advice *Discuss with Haematology lead to take to MDT*
Pulmonary Hypertension	Routine echocardiogram, every 1 – 3 years, specifically asking for TRV	Raised TRV (>250 cm/sec)	Pulmonary hypertension clinic *Refer to Dr Nicky Gray*

Respiratory	Chronic lung problems (without known cause eg asthma) note history and request CXR / CT scan of chest as appropriate. If chronic low baseline oxygen, request lung function tests, sleep study and high-resolution CT scan.	According to investigation results or if suggestive of bronchiectasis or tuberculosis If sleep disordered breathing	Refer to Respiratory Team *Respiratory SpR or Consultant on call via Alertive if urgent, or outpatient referral* Refer to Sleep Apnoea clinic *Outpatient referral letter*
Ulceration	Check appearance, take swab for MC&S, advise daily cleaning with saline solution, application of non-adherent dressing, firm strapping and elevate. Antibiotics to treat clinical infection / cellulitis.	If not healing, deep, slough covered, heavy exudate. Discuss with Consultant Microbiologist.	Tissue viability service via the GP *x6653 or TvnTeam@nnuh.nhs.uk or Alertive role* Consultant Microbiology *x4587*
Endocrine			
Endocrinology	LH, FSH, testosterone / oestradiol R2 MRI scan of liver Bone mineral density scan (DEXA)	Abnormal findings or concerns	Referral to endocrinology *Outpatient referral or Endocrine SpR on call via Alertive*
Infection			
Infection	Fever, rigors, MS&C, treat	Discuss with microbiology if unresolved or problematic.	Referral to Consultant Microbiologist *x4587*
Neurology			
Neurological problems	TIA / stroke usually presents acutely BUT may give history of TIA or other neurology as outpatient. Full	Always refer.	Referral via pathway for stroke services

	neurological examination, request CT scan of brain + contrast		*Stroke CNS x6588/6516 Stroke Alert Nurse on Alertive*
Ophthalmology			
Retinopathy	Screen according to genotype and degree of retinopathy. Patient report acute change in vision.	Routine screen. Urgent referral	Ophthalmology *Outpatient referral via letter* *Eye Clinic x3787 (out of hours on call Dr by switchboard)*
Orthopaedic			
Orthopaedic problems	Examine range of movements at affected site. If pain in one joint for > 1 month – plain X ray and review with results. If no abnormalities seen but pain persists, request MR scan.	If evidence of AVN or impingement syndrome	Orthopaedic service *Urgent: On call Orthopaedic Surgeon via Alertive or switchboard* *Non-urgent: outpatient referral*
Osteomyelitis	Fever, painful swollen limb with limited range of movement. Patient reports pain different to normal VOC. Inflammatory markers, Ultrasound, MRI. Start antibiotics (eg ceftriaxone).	Always	MDT Orthopaedic, red cell and Microbiologist *Contacts as above*
Outpatient			
Annual Review	Ensure patient has access to annual review appointment	Annual appointment with SHT	*Adults – book in HAEBY clinic via Dr Docherty Children – annual review at CUH*
Routine out patient appointments			*Adults – Haematology Secretary x3866* *Children – Secretary x3622*
Travel / DWP / Employer / education			*Contact patient's consultant*
Pain			
Chronic pain	Often managed by Red Cell team in outpatient setting. Important to identify patients with ongoing and multifactorial pain requiring	Referral to Red Cell Psychologist for help with non-pharmacological interventions.	Referral to red cell psychology service

	increasing medication, opioids.	Referral to MDT chronic pain team might be beneficial eg local nerve block etc	Referral to Pain Team *Outpatient referral letter*
Renal			
Renal Disease	U&E, creatinine, eGFR, Urine PCR, Calcium, phosphate, uric acid, renal tract ultrasound. (eGFR >90mls/min urine PCR 50 – 100 mg/mmol start on ACE inhibitor).	Urine PCR >100mg/mmol. Hypertension > 140/90. Declining e-GFR / rising creatinine.	Renal Service *Inpatients – Renal SpR on call via Alertive* *Outpatient referral letter*
Haematuria	Urinalysis, MSU, US renal tract / IVU. UTI antibiotic treatment locally or via GP.	Haematuria not resulting from simple resolved UTI.	Urology team *Inpatients – Urology SpR on call via Alertive* *Outpatient referral letter*
Sexual Health (Obstetrics / Gynaecology / Urology / Fertility)			
Priapism	Check with male patients routinely. Stuttering priapism, suggest emptying bladder, hydration, oral analgesia, warm bath and exercise. Trial of medication: Ephedrine 15-30mg OD nocte or Etilefrine 25-50mg OD nocte.	If symptom continues despite these measures. Urgent referral for patient who attends A/E due to prolonged priapism.	Urology team *Inpatients – Urology SpR on call via Alertive or switchboard* *Outpatient referral letter*
Fertility	Encourage partner testing Usually refer patient to GP	Referral to specialist counsellors if potential of SCD baby	Red cell counsellors *Discuss with Dr Docherty in Haematology* Fertility services *Via GP to Bourne Hall*
Obstetric	Patient reports pregnancy. Ensure all red cell team aware. Pregnancy test.	Always	Specialist Obstetric red cell team *Dr Mark Andrews, Obstetric Physician and add to Maternal Medicine MDT*
Transplantation and novel treatments			

Transplantation	Meets transplantation criteria and / or patient request.	Local and HCC discuss, referral to NHP.	Transplantation centre for red cell patients. *Discuss with Dr Docherty (adults) or Dr Ponnampalam (children) for referral to Red Cell MDT*

	Consider HLA typing patient and family members.		
Blood Transfusion	Samples in line with local policy. Ensure full red cell phenotype / genotype available.	Multiple red cell antibodies. Rare phenotypes / genotypes where number of units requested are not readily available. Transfusion reactions (local team to determine if NHS Blood and Transplant need to be informed.	Local Hospital Transfusion Team *Via Dr Docherty, Haematologist* NHS Blood and Transplant *Via Blood Bank x2906*
Hydroxycarbamide	Discuss with all patients; ensure monitoring.		*Monitored in regular outpatient clinics in Haematology or Paediatrics*
Novel treatments	Meets criteria and / or patient inquiry.	Local and HCC discussion at MDT.	HCC / NHP *Useful team will discuss at Red Cell MDT*

Appendix 5: Sickle Chronic Lung Disease – Staging Criteria

Clinical Markers	Stage 1	Stage 2	Stage 3	Stage 4
Chest pain	Recurrent substernal pain and chronic cough	Increased pain over stage 1	Severe midline crushing pain.	Severe and prolonged pain with dyspnoea at rest.
Blood gases	Normal oxygen saturation	Normal oxygen saturation	Hypoxia with partial pressure oxygen (9.5 kPa) during stable periods	Hypoxia with partial pressure oxygen (8.0 kPa) during stable periods
X-Ray	Decreased distal pulmonary vascularity, hyperexpansion, evidence suggestive of increased interstitial markings	Diffuse, fine interstitial fibrosis involving all lobes of the lung	Pulmonary fibrosis	Severe pulmonary fibrosis
Pulmonary function tests	Decreased FVC, TLC, FEV_1 and FEV_1/FVC ratio (mild, 80% of predicted normal or 1 SD below normal)	Decreased FVC, TLC, DCO, FEV_1 and FEV_1/FVC ratio (moderate, 60% of predicted normal or 2 SD below normal)	Decreased FVC, TLC, DCO, FEV_1 and FEV_1/FVC ratio (severe, 40% of predicted normal or 3 SD below normal)	Patient frequently unable to complete testing due to degree of hypoxia
ECG and ECHO	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement. Progressive increase in heart size.	Severe right ventricular and right atrial hypertrophy. Ischaemic T waves in V1 and V2 and cor pulmonale

Appendix 6: Summary Incentive Spirometry in adults with SCD

Patient Selection

All patients who fulfil one or more of the following criteria:

- Acute chest or back pain above the diaphragm.
- Receiving opiate analgesia.
- Clinical signs of respiratory infection.
- Red Cell Team specifically requests.

Initiation of I.S. Programme by admitting doctor

- Document selection in medical notes.
- Inform the nurse in charge of the ward.
- Refer any patient with signs of respiratory infection to the physiotherapist.
- The nurse allocated to the patient has responsibility for ensuring that the programme is commenced, and results documented.

Incentive Spirometry (I.S.) programme

- **10 maximal inspirations** using incentive spirometer every 2 hours between 08.00 hr and 22.00 hr and while awake at night.
- The patient should be sitting in an upright position.
- Patients requiring > 35% oxygen should continue with oxygen therapy via nasal specs during I.S. breathing.
- The maximum inspiratory capacity achieved, pain score and SaO2 should be recorded in the patient's clinical record.

Discontinuation of I.S.

The Red Cell Team should consider discontinuing I.S. if:

- The patient is unfit to continue for medical reasons.
- The chest and / or back pains have subsided.
- Opiate analgesia has been discontinued.
- There are no clinical signs of respiratory infection.

Appendix 7: Travelling / Flying and SCD

Information for patients

Whereas most people with SCD have travelled by air many times without any problems, the prolonged exposure to lower oxygen levels at cruising altitude can trigger a crisis. These crises can be mild or severe and may happen during the flight or a few days later. It is important **not to travel by air within 10-14 days of a sickle cell crisis**.
The Civil Aviation Authority (CAA) recommends that all patients with SCD (HbSS or equivalent) should travel with or have access to supplementary oxygen for the entire duration of the flight.
Most airlines will be able to supply oxygen to passengers on flights longer than 5-6 hours for free, provided that the **passenger will inform the airline in advance.** Most airlines limit the supply of oxygen to a few passengers, sometimes only to one passenger per flight. If that is the case, the **passenger will need to arrange for their own portable oxygen** and inform the airline about their arrangements.
In brief, we recommend taking the following steps:

1. Discuss the need for supplementary oxygen well in advance with the red cell team.
2. Make sure you have appropriate travel insurance, covering medical costs abroad and/or repatriation. The Sickle Cell Society has published a list of insurers on their website that offer fair packages for people with SCD.
3. Before booking contact the airline about the need to travel with oxygen.
4. If the airline indicates that they can't provide oxygen on board, it is your own responsibility to contact a supplier of portable oxygen and make any necessary arrangements.
5. The airline may provide you with a form part of which will need to be completed and signed by a senior member of the red cell team.
6. Think about and discuss with the red cell team what medication you may need to take with you and whether you will need a letter to confirm that the medication (particular if opioids are to be carried) is necessary, for example to show at customs / border control.
7. It would be sensible to travel with a copy of your last annual (comprehensive) review letter just in case you need to access health services while away from so that the medical staff have details of your condition and treatments.

Example of a travel letter for the patient to carry:

Red Cell Team Clinical Haematology
TO WHOM IT MAY CONCERN
Re : *{INSERT PATIENT'S DETAILS}*
The above named is under the care of the specialist red cell services for a clinically significant Sickle Cell Disorder (SCD). Sickle cell is an inherited condition in which as well as anaemia there may be painful "crisis" affecting the bones or other organs. For this reason, he/she carries a small supply of strong painkillers and other medication necessary for their condition. {*include a list of medication the patient will be travelling with}.* These are strictly for medicinal purposes and should not give rise to any concern. This patient is normally well, and there should be no problems during the flight provided the right preventive measures are taken.

- They should be offered a drink frequently, at least hourly, as dehydration can precipitate crises.
- They should be allowed to mobilise freely, when flight regulations allow.
- If there is any suggestion of falling oxygen levels, they must be given inhaled oxygen immediately.

I would not expect them to experience any problem during the flight, but it would certainly help if the above could be observed.
{Delete or include as appropriate}

- As the flight is over five hours it is recommended that this patient travels on oxygen for the entire duration of the flight (CAA Guidelines). We have recommended to the patient that they inform the airline in advance about this requirement.
- The patient has been optimised for travel, receiving a blood transfusion in advance of travel and therefore we would not anticipate any difficulties.

Yours faithfully

{Name; position and hospital and contact details}

Appendix 8: Example for employers / DWP or further education institutions

Below is a generic letter that can be used as a template for patients to give to employers, tutors or to support housing and benefit applications. It is not possible to cover everything but it is hoped that below can provide some common themes. In addtion the patient may wish to submit a copy of their last comprehensive annual review letter which will contain specific individual complications.

Red Cell Team Clinical Haematology **TO WHOM IT MAY CONCERN**

Re : *{INSERT PATIENT'S DETAILS}*

Sickle cell is an inherited disorder of the haemoglobin (red blood cells); it is the commonest inherited single gene disorder in the UK. Sickle Cell Disorders (SCD) are inherited in an autosomal recessive pattern, when a mutation is inherited from both parents the haemoglobin, the oxygen carrying pigment in the red blood cells, if affected. When exposed to low oxygen conditions, the haemoglobin distorts and the red cells become stiff, misshapen ("sickled") and sticky. They cannot squeeze through the smaller blood vessels in the circulation and stack. The blood vessel become blocked, referred to as a "crisis", which causes severe pain and damage to the tissues and organs. Any organ and tissues can be affected the lungs "chest syndrome" or the brain causing a stroke. The crises can have a trigger, infection, cold / drafts, over exertion, stress but sometimes occur without any precipitant. A person with a SCD is also prone to infections and anaemia. To reduce the risk of a crisis and to aid continued health it is helpful to offer understanding and support. It might be useful to consider the following:

- Consideration about mobility and comfort.
- What to do if the employee / student has a sickle cell crisis at work / in class
- Adjustment to ensure workstation / class room is draft free and warm.
- Adjustment to allow good and continued hydration.
- Safe, secure access to medication
- Reasonable adjustment to manage absences due to illness and time off for appointments,
- Flexibility to allow for their condition.

The individual having a crisis could become suddenly unwell and / or complain of severe pain. **If you suspect an employee / student with sickle cell is having a crisis, you may need to assist with arrangement to get them urgent medical treatment.**

More generic information and support can be sought from the Sickle Cell Society (www.sicklecellsociety.org).

Yours faithfully

{Name; position and hospital and contact details}

Appendix 9: Hydroxycarbamide (Hydroxyurea) Information Sheet

Introduction

It is recommended based on evidence of improved life expectancy, reduced sickle damage to organs, less need for blood transfusion and a reduction in the frequency and severity of pain cirises that hydroxycarbamide is offered to EVERYONE with HbSS, or Hb Sβ^0 thalassaemia. The medication was introduced in the 1990's and works by increasing the production of fetal (baby) haemoglobin which is the predominant haemoglobin in newborns. This fetal haemoglobin (HbF) is normally present at low levels in adults but if it can be increased it can reduce sickling. We know that sickling doesn't occur in newborn babies and adults with sickle cell who have naturally high levels of HbF have fewer pain episodes and other complications. In addition hydroxycarbamide reduces the stickiness of the red blood cells which can also be beneficial. A large multi-center study conducted in North America published in 1994 reported 80% of patients showed fewer and less severe painful crises. The study also showed a decrease in mortality and a reduction in sickle damage to vital organs such as the kidneys and liver. People who have other types of sickle cell disease for example HbSC, Hb Sβ^+, may benefit from taking hydroxycarbamide as well but there are fewer research studies, so the evidence is not so clear-cut.

What is Hydroxycarbamide?

Hydroxycarbamide is a drug that has been used in the treatment of different blood disorders for decades.

How does it work?

It is thought that hydroxycarbamide appears to work in a number of ways:

- It increases production of fetal haemoglobin although this can take some weeks or months.
- It decreases the stickiness of the young red cells which can reduce the risk of a crisis, this can happen quite quickly after starting the medication, about a week.
- It reduces the number of white blood cells in particular neutrophils, which are often raised in number in people with severe sickle cell. This may be important because the white cells produce chemicals that can cause inflammation and might speed up sickling. Having fewer white blood cells makes this less likely.
- It improves levels of a chemical called nitric oxide in the blood; this helps the walls of the blood vessels to relax and so can help improve blood flow.

How do you take it?

Hydroxycarbamide comes in 500mg capsules that you take once a day by mouth. You begin at a low weight-related dose, and are monitored to see the response. Then usually the dose will be slowly increased until it is the most effective for you.

What problems or side effects does it have?

All medication can have side effects; even drugs such as aspirin and paracetamol, which people think of as safe, can occasionally cause serious problems. The risks associated with Hydroxycarbamide are low, but it has some side effects that you should be aware of:

a) It can cause a fall in your red cells, white cells or platelets. For this reason you start on a low dose, working up to the dose that you need with regular blood tests on starting and when the dose is increased to monitor that the number of these cells isn't falling. If at any stage your blood counts fall, your will stop the medication and then, when the counts recover, restart at a lower dose.

b) When you are on hydroxycarbamide if you become unwell (sore throat, cold like symptoms, signs of infection or have a temperature (38^{o}C or above) you should stop the hydroxycarbamide, arrange for an urgent blood test (via the Emergency Department if outside normal working hours) and inform a member of the Red Cell Haematology Team (key contacts will be provided). This is important to establish whether the number of white blood cells, that fight off infections are of an adequate level.

c) It often causes some mild darkening of the skin and nails.

d) Although the following are uncommon it can lead to stomach or bowel disturbance and / or to hair thinning.

e) It is important that you do not become pregnant, or make your partner pregnant, while you are taking Hydroxycarbamide because it is possible that it could harm the baby. If you are planning to start a family you should stop taking Hydroxycarbamide for 3 months prior to becoming pregnant.

f) Although Hydroxycarbamide does not affect sexual function there have been concerns that the drug may affect the sperm produced in men, however severe sickle cell can cause this problem and many male patients who have been taking the medication haven't had any problems with pregnancy. Some red cell services have offered semen analysis and even sperm storage but this is not routine.

Now you have read this leaflet please discuss with friends and family and do your own research. The red cell team will be happy to discuss and to answer any questions you have about this treatment.

Appendix 10: Example of Specialist Patient Care Plan

ADULT SICKLE CELL: SPECIALIST PATIENT CARE PLAN (sPCP)

Patient name: *Insert first and surname of patient*	**Patient DOB:** *Insert patient DOB*	**Hosptial Number:** *Insert local hospital number*
Patient NHS number *Insert the patient's NHS number*	**Patient usually attends:** *Insert the name of hospital attended / where sPCP completed*	
Approximate weight *Insert weight in Kg and date weight checked*	**Approximate height** *Insert height in cm and date height taken*	
Diagnosis: *Please insert the patient's diagnosis OR delete as appropriate* **Hb SS Hb SC HbSβ^0**		
Allergies: **NKDA** *OR delete and insert any allergies*		
Baseline Values *insert the patient's baseline values below – approximate mean of results in well state; out patienr results, not A/E or in-patient results.*		
Hb (g/l)	**Bilirubin (umol/l)**	**Reticulocytes (%)**
Creatinine (mg/dl)	**LDH (iu/l)**	**Oxygen saturations (%) on air:**

Complications / Concerns / Issues

Insert any complications and /or problems that are important for staff to be aware of should the patient present acutely; for example:

Previous stroke

Previous chest crisis

Episode of hyperhaemolysis / DHTR – CAUTION if transfusion required

For more information please refer to the patient's last comprehensive out patient annual review.

A/E and in-patient pain management (see Appendix C for acute presentation summary)

Pain management for acute admission should be agreed, and reviewed annually, with the patient in outpatients. Below are GENERIC EXAMPLES which can be considered (delete as appropriate); refer to local availability and guidance

ORAL MORPHINE

Good option for patients who infrequently attend, particularly younger patients who have recently graduated from paediatric services. Doses in line with local BNF policy.

MORPHINE (usual first line)

0.15mg/kg subcutaneously (SC) stat for immediate pain relief reassess after 30 minutes give 50% of initial dose next and reassess after a further 30 minutes.

eg 70 Kg x 0.15 = 10.5 so 10.5mg stat additional 5.25 after 30 minutes if pain not alleviated: 15 mg hourly

Anti-emetic – state type and dose in line with local policy.

OR

DIAMORPHINE (if available previously used)

0.1mg/kg subcutaneously (SC) stat for immediate pain relief reassess after 30 minutes, give 50% of initial dose if only partial relief is achieved and reassess after a further 30 minutes.

eg 70 Kg x 0.1 = 7 so 7mg stat additional 3.5 after 30 minutes if pain not alleviated: 10mg hourly

For ease and to reduce wastage usual doses are 5 / 10 / 15 up to a max of 20 mg stat

Anti-emetic – state type and dose in line with local BNF policy.

IF CANNOT TOLERATE MORPHINE OR DIAMORPHINE

Consider OXYCODONE *immediate release if cannot tolerate diamorphine or morphine dose in line with local BNF policy.*

Information on pain management weening to oral and suggestion for discharge

Include usual plan for reduction in dose and direction regarding use of PCA pump. Include routine pain medication to be offerred at discharge if admitted.

REVIEWER and DATE: *Insert name, position of person and date completing/ reviewed*

Appendix 11: Example Comprehensive Annual Review Proforma

Hospital Number:				Date:
Last Name:		First Name:		
Date of Birth:	Diagnosis:		NHS #:	
Height(cm)	Weight(kg)	O_2 Sats	Pulse	Blood Pressure
Number of A/E attendances:		Number of unscheduled inpatient admissions:		
Number of bed days in hospital:		Number of planned day case attendances:		
Comorbidity		New Comorbidity		
Allergies				
Patient specialist pain plan	Analgesia at home / hospital: Protocol available Y / N Changes required Y / N (indicate change/s below)			
Regular Blood Transfusion	ARCE / Top up	No. of units lifetime		
No. units in lasts 12 months		Hospital where transfused		
Red cell antibodies / any reactions?				
Patient consents to transfusion?	*Benefits and risks discussed* YES / NO			

Vaccinations in this Review Period				
	Annual Influenza		Meningitis B	
	Hepatitis B		Meningococcal B	
	Hib / Meningitis C		PCV13	
	Meningitis ACWY		PPV23	

Mental health			
Patient mood score / discussed:	YES/NO	Psychology service already accessed / OK? :	YES/NO
New referral to psychology services to support required:	YES/NO	Patient required other mental health support services:	YES/NO
Patient accessed Haemoglobinopathy community services	YES/NO	Patient engagement support groups	YES/NO
Treatment			

Eligible for hydroxycarbamide	YES/NO	Offered / taking hydroxycarbamide	YES/NO	Declined hydroxycarbamide	YES / NO
Penicillin prophylaxis	YES/NO	Penicillin treatment dose if unwell	YES/NO	Folic Acid	YES/NO

Iron chelation required	YES/NO	Iron chelation	*Type and dose*	Changes required	YES/NO
Novel treatment discussed / considered	*Voxelotor, SCT / BMT, other*				
Patient discussed at National MDT panel:	YES/NO				
Fathered a child this review period	YES/NO	Pregnancy this review period	YES/NO		

Investigations Type	Date	Result
Pulmonary Hypotension Screen		
Echocardiography (TRV / PASP)		
AVN check		
Ophthalmology assessment		

Specialist Imaging	Date	Result
Ferriscan Liver Iron (mg/g/w)		
MRI Hip / Shoulder (AVN)		
Other		

Test	Date + Results	Test	Date + Result	Test	Date + Result
Hb		Bilirubin umol/l		HbS% (if applicable)	
Mean (steady state Hb)		ALT u/l		HbS+C% (if applicable)	
Neutrophils x 10^9/l		Creatinine		HbF% (if applicable)	
Platelets x 10^9/l		Vitamin D			
Reticulocyte %		LDH			
		Urine PCR		Ferritin	
HCV		TFT		Transferrin saturation %	
HBV		eGFR			
HIV					
HBsAb					

Enter any other blood test results required in spaces. Note: Patient transfused in last 3 months date of transfusion:

Current issues:

Discussion and actions:

Completed by:.....Date:

Appendix 12: Information on Pain in patients living with sickle cell

The acute painful episode, or crisis, is the characteristic presentation of patients with sickle cell disorders (SCD). These episodes can occur unpredictably, often without clear precipitating factors (aggravating factors include infection, dehydration, cold, damp, emotional stress, unaccustomed exercise). Pain can fluctuate in intensity and duration, ranging from mild to severe and debilitating. The acute painful episode is the most frequent cause of hospitalisation, accounting for more than 90% of hospital episodes but the majority of acute painful episodes are managed within the community.

There is no specific test that confirms whether the patient is in a sickle cell crisis or not, regard the patient (and/or their carer) as an expert in their condition. Patients can usually differentiate what is sickle pain from what is not.

Patients who present with a painful crisis (also referred to as vaso-occlusive crisis or VOC) should be treated as an **acute medical emergency** and adequate analgesia should be offered within 30 minutes from presentation (NICE, 2012) like is applicable to all other causes of acute severe pain.

The Pain in Sickle Cell Epidemiology Study (PiSCES) concluded that pain in SCD was far more prevalent and severe than previously thought with most patients managing their pain at home. Adult patients in this American single site study reported experiencing pain on 54.5% of the surveyed days; with 29% of patients experiencing pain on more than 95% of the days. Whilst this study did not distinguish between acute and chronic pain it does suggest that many patients experience pain on most days. Another American study of adult patients with SCD reported 92% of patients experienced pain lasting from 6 months to 2 years with 90% taking pain medication daily for a period of 6 months. There is little robust evidence about the management of SCD chronic pain, so most of the following is derived from general guidance on the management of chronic pain and prescribing in non-cancer chronic pain. Alongside medication-directed management, there is increasing support and recommendation for working within a multidisciplinary team (MDT) in managing chronic pain, including therapeutic interventions such as psychology and specialist pain physiotherapy, rather than depending on pharmacological therapy alone. Through engagement with the MDT, people living with SCD can be supported in acquiring and developing skills in pain management, including managing unhelpful or difficult thoughts, managing difficult emotions including anxiety, stress and worry, pacing activities, moving and exercising in the presence of SCD and mindfulness and relaxation strategies.

SCD patients with chronic pain are often dependent on regular opioid analgesia. Whilst the analgetic effect is often adequate, there are some serious problems with the long-term use of opioids:

- Increasing quantities of oral opioids often do not help.
- There is little evidence that long-term high-dose opioids (typically defined as 90 mg of morphine equivalents per day) improve pain or function but plenty of evidence that they cause harm. Opioids can trigger mast cell degranulation causing pain and pruritus; increase Nitric Oxoid resulting in vasodilation and can, particularly when administered subcutaneously, lead to delayed wound healing, kidney injury, retinopathy and vascular permeability.
- Chronic pain in adults follows an exacerbating/remitting course and could necessitate that the patient take the dose on “good” days simply to prevent withdrawal.
- Analgesia in situations of acute-on-chronic pain in patients on long-term opioids is challenging because of high levels of tolerance.
- High-dose opioid use can lead to paradoxical hyperalgesia.

Oral analgesia is preferred. However, parenteral (or intranasal if available) administration has a more rapid onset of action and may be necessary at least initially. Intravenous injection has a very rapid effect but has the drawback of requiring venous access. Most opioid drugs are as effective by subcutaneous injection as by intramuscular. Although

intramuscular administration has a swifter onset of action repeated use of this route can result in muscle

necrosis and / or the formation of chronic, painful abscesses. Of note oxynorm should only be administered orally or subcutaneously; not intramuscularly. Each of the morphine derivatives has its own pros and cons. Morphine is a good choice for both oral and parenteral treatment. Diamorphine (Heroin) is essentially a pro-drug of morphine and as such there are no significant differences in the pharmacodynamics of diamorphine when compared to morphine when used for acute pain. However, diamorphine has the advantage that it can be dissolved in a smaller volume of diluent (less than morphine) and has a better lipid-solubility allowing s.c. infusion, which is particularly useful in patients with poor IV access. There are concerns that diamorphine gives the highest level of euphoria of all opioids and contributes to dependency and difficulties with weaning. The UK is the only country in the world where the production of diamorphine is not illegal. At the time of writing of this guidance, there are significant supply issues and for this reason and the concerns mentioned above, diamorphine is not first choice.

Oxycodon is available as a second line opioid available for patients unable to tolerate oral or subcutaneous morphine. **Immediate release, modified release and injection preparations have similar names. Take care when prescribing, dispensing or administering morphine or oxycodon. Should be avoided or used with caution in patients with liver or renal impairment.**

There is no agreed evidence-based guideline on the weaning of analgesia in patients with SCDs. A typical painful episode lasts between 3 and 7 days, but especially in older patients can take longer to settle. The analgesic requirements may vary from individual to individual and a common-sense approach is required to achieve a successful transition from the hospital setting to ambulatory care with adequate pain relief. Long-term opioids should be avoided as much as possible in order to reduce the risks of tolerance and dependence. General principles include:

- Do not reduce opioids during the first 24 hours unless there is respiratory depression or increased lethargy.
- Reduce the DOSE rather than the FREQUENCY. Patients often request to discontinue parenteral morphine at once but this approach is more likely to cause rebound or withdrawal symptoms with a risk of readmission.
- Typically, reduce the dose by 10-20% at the time (regardless of way of administration).
- Avoid reducing the opioid dose during the night when pain assessment is suboptimal
- Convert to oral medication in a dose equivalent to the parenteral dose as soon as possible.

Barriers to effective pain management in sickle cell disease:

Patients with SCD often receive suboptimal treatment of an acute painful episode with audit data showing time to analgesia significantly longer than 30 minutes recommended with dosing insufficient leaving the patient in severe pain. Factors like staffing levels and ED capacity play a role, several studies have identified specific barriers to the treatment of the acute painful episode in SCD which result in mistrust and reinforces negativity:

- **Negative provider attitudes** that interfere with assessment and treatment include:
- SCD patients exaggerate their pain.
- SCD patients are dishonest and manipulative.
- SCD patients are uncooperative and frustrating to manage.
- People with SCD are addicted to opioids. While 2-5% of the SCD population may have an opioid dependency problem, > 95% do not. The small number that do are likely to attend frequently and this will contribute to bias.
- **Patient-related factors**: Manifestation of vaso-occlusive pain which is complex and multifactorial. Children often have swollen hands or feet (visible sign) but in adolescents and adults there may not be a ‘visible’ sign and the pain may be compounded with regional pain syndromes, avascular necrosis, neuropathic pain, depression, opioid-induced hyperalgesia.
- Patients who attend frequently remain at risk of SCD related complications and must be assessed as outlined in section ‘Acute Presentation’. Under certain circumstances restrictions may be in place for individual patients this is summarised in the specialist PCP.

The Red Cell Network
Haemoglobinopathy Coordinating Centre

Appendix 13: SCD patients prior to elective surgery

Hb>90g/l, mild phenotype and minor-moderate risk surgery: no transfusion If severe phenotype or high risk surgery: Exchange blood transfusion 2-10 days preoperatively, aim at Hb around 100g/l and Hb S+C% <60%.	HbS/C disease	Hb<90g/l and minor-moderate-risk surgery: Top-up transfusion 2-10 days preoperatively. Aim at Hb around 100 g/l. High risk surgery: Exchange blood transfusion 2-10 days preoperatively, aim at Hb around 100g/l and Hb S+C % <60%.

For patients already on an exchange blood transfusion programme, their next exchange transfusion needs to be scheduled within 2-10 days from their surgery.

The transfusion lab needs to be informed about blood needed for sickle patients, for top-up or exchange blood transfusion, in order to accommodate special requirements (sickle-negative blood, fully phenotypically matched). More time will need to be allowed in case of all antibodies.

Careful consideration will need to be given to cases with a history of hyperhaemolysis.

Appendix 14: Example of MDT proforma

HAEMOGLOBINOPATHY MDT PROFORMA			
MDT date		Patient name	
Referral hospital		Hospital No.	
Referral Consultant		NHS No.	
MDT Number (Admin use only)		DOB / Age	
New patient or Follow up (delete)		Sex	Male / Female
Patient Diagnosis (Genotype)			
Past Medical History / Complications			
Question for MDT			
Scans / results required	Yes / No	Attached	Yes / No
MDT Review Outcome			
Treatment Plan / Actions			
Authorised by / Attendees			

Insert here method of referral and who to refer to; usually discuss locally, include decision; if necessary refer to SHT / HCC MDT; include decision; refer to NHP https://www.nationalhaempanel-nhs.net/mdtfunction

Appendix 15: SCD patient presents with stroke summary flowchart