Management of Adults with Thalassaemia

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

They exist to standardise care for adults with Thalassaemia within the London, South Central and South-west England 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

Introduction

Thalassaemia is a genetic disorder which results in impaired haemoglobin production, ineffective erythropoiesis, anaemia and bone marrow expansion due to a reduction, or absence, of alpha and/or beta globins required for the normal production of adult haemoglobin (HbA). Inheritance is in an autosomal recessive pattern. Thalassaemia is most commonly in families originally from the Southern Mediterranean, middle East, South and South-East Asia. There has been inequity of standards of care in the UK, in part due to the rarity of the condition and the geographically uneven distribution. Thalassaemia is a complex disorder and good management is reliant on clinical and laboratory expertise incorporating a multidisciplinary and holistic approach. This document provides an overview of essential care and must be used in conjunction with the support of specialist teams with experience and expertise in these disorders. Should a patient present at a hospital that is not their routine specialist centre it is important to contact and involve their external red cell team.

Thalassemia is classified based on clinical phenotype. Transfusion dependent thalassemia (TDT), previously known as thalassemia major, indicates that the patient requires regular lifelong red cell transfusions. Non-transfusion dependent thalassemia (NTDT), previously known as thalassemia intermedia, may require intermittent, regular or no red cell transfusions depending on whether the patient develops complications. Both these disorders will largely be as a result of mutations in the beta globin genes with or without accompanying alpha globin gene mutations. Haemoglobin H (HbH) disease is when there is only one out of four functioning alpha globin genes, and patients are often classified as NTDT however it is important to note that patients may move from NTDT to TDT. There are over 2000 in the UK living with thalassaemia; approximately 750 with TDT (NHR Annual report 2022-2023).

The mainstay of treatment in TDT is red cell transfusion therapy typically to maintain a trough haemoglobin (Hb) of 95g/L-105g/L usually given as 2-3 units 3-4 weekly. Iron excess, partly due to regular blood transfusions but also due to ineffective erythropoiesis, causes iron accumulation in organs including the heart (cardiac iron), liver (liver iron, fibrosis, cirrhosis and liver cancer), endocrine organs (growth failure, infertility, hypothyroidism, bone disease, hypoparathyroidism) and diabetes. Good chelation therapy, to mitigate iron loading, is the mainstay of treatment to prevent such complications without which patients will have significant medical complications and, if allowed to go unchecked, may die. People who have good transfusion and chelation care from an early age should be expected to be largely healthy with minimal complications. However, older patients from high income countries, patients who do not comply with treatment recommendations and patients arriving from lower income countries may not have had effective transfusion or chelation regimens often have significant complications relating to iron overload and / or more restrictive transfusion regimens. In high income countries the threshold for converting patients from NTDT to TDT is much lower. As such, many patients with NTDT or those who were converted to TDT later than would have been optimal, have complications of their disorder which could have been avoided with regular transfusion and good chelation regimes.

All adults living with thalassaemia should receive regular follow-up to detect the emergence of chronic complications and to implement appropriate timely management. At a minimum every patient must have a comprehensive annual review by a Consultant or equivalent from the red cell team. Management is predominantly out-patient based but occasionally patients present as acute emergencies. An integral part of routine care should be a focus on self management and patient education. The patient should be taught how to manage their disorder well, how to navigate healthcare and situations that may impacted their health. Patient will often form strong attachments with their specialist teams, having known them for their entire lives. Professionalism is key to good patient care and **patients should benefit from the expertise, kindness and compassion they deserve. Unhelpful attitudes from healthcare workers can have a negative impact on their lifelong care.** The four key NHS principles of **respect, dignity, compassion** and **care** are key.

Whilst specialist care is an important cornerstone of thalassaemia care, the General Practitioner (GP) should be the first port of call for unrelated ailments. The GP should retain the responsibility for all other

routine activity that is provided by primary care e.g. vaccinating patients and also for prescribing all routine medications with the exception of medication that requires specialist monitoring and administration, for example iron chelation; screening programmes; non thalassaemia disease monitoring. GPs should be encouraged to contact the red cell team to discuss individual patients and / or to attend MDT meetings where it would be helpful.

Service provision in England

NHS England commission specialist haemoglobinopathy services with a dedicated Clinical Reference Group (CRG) for the care of patients with thalassaemia and other inherited red cell disorders. Patient care is organised via a National Haemoglobinopathy Panel (NHP) https://www.nationalhaempanel-nhs.net, four thalassaemia Haemoglobinopathy Coordinating Centres (HCC) over 25 Specialist Haemoglobinopathy Teams (SHT) and a number of 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 clinically significant thalassaemia 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 the NHP usually in the context of a multidisciplinary meeting. Services are reviewed by the Haemoglobinopathy Peer Review process against document quality standards (https://haemoglobin.org.uk/3d-flip-book/health-services-for-people-with-haemoglobin-disorders- standards-2021/). There is a national data base of patients with inherited red cell disorders, the national haemoglobinopathy register (NHR), https://nhr.mdsas.com/ which contains information such as their SHT/LHT/HCC, demographics, disease type, immunisations, annual review and comorbidities. The introduction of the NHR has transformed the ability for red cell data management teams to provide key dashboard, audit and research data.

While this document outlines care in adult patients it is important to have an understanding of care prior to transfer to the adult services. Patients born in the UK are identified as having thalassaemia via neonatal screening and although some patients undergo curative transplant procedures, most do not. Most children who are transfusion dependent will start regular transfusion and subsequently chelation in early childhood and sometimes in infancy. A robust structure for transition of patients from the paediatric to the adult services should be in place.

Summary

This guidance applies to **all staff**, medical, nursing and allied health professionals who are involved with the care of patients living with thalassaemia. Key principles are to:

- Be aware and sensitive.
- Monitor correctly
- Treat promptly, 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 team 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 thalassaemia. The term 'thalassaemia' used in the guideline refers to all patients TDT and NTDT (as outlined in the introduction 1.0 above). The term adult is used to describe any patient under the adult red cell service, usually 16 years of age and above.
The guideline excludes:

- Sickle β-thalassaemia, a sickling disorder which should be managed according to the guidance on management of Sickle Cell Disease.
- Patients with β- or α-thalassaemia trait as these are carrier states and not clinically significant.
- There are other rarer inherited red cell disorders which can cause transfusion dependence or the need for intermittent transfusions including Diamond Blackfan anaemia and Pyruvate kinase deficiency. The specifics and pathophysiology are not covered here.

The document is based on the 2023 Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, UK Thalassaemia Society 2023.

Inheritance

Detail on phenotypes, genotypes and inheritance are not included within this guidance. For further information refer to Chapter 3 of the Standards for the Clinical Care of Children and Adults Living with Thalassaemia (UKTS, 2023).

References

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Abbreviations and terminology

AXR	Abdominal X Ray
ACE inhibitor	Angiotensin converting enzyme inhibitor
ECG	Electrocardiogram
ED	Accident and Emergency or Emergency Care Department
CBT	Cognitive Behavioural Therapy
CMV	Cytomegalovirus
CNS	Clinical Nurse Specialist
CRP	C-reactive protein
CT	Computerized Tomography scan
CVC	Central Venous Catheter
CXR	Chest X Ray
ECHO	Echocardiography
eGFR	Estimated Glomerular Filtration Rate
FBC	Full Blood Count
HCC	Haemoglobinopathy Coordinating Centre
Hb	Haemoglobin
ICU / HDU	Intensive Care or High Dependency Unit
LHT	Local Haemoglobinopathy Team
LMWH	Low Molecular Weight Heparin
MC&S	Microscopy, culture and sensitivity
MDT	Multidisciplinary Team

- MRCP Magnetic resonance cholangiopancreatography
- MRI Magnetic resonance imaging
- 6MWT 6 minute walk test
- NHP National Haemoglobinopathy Panel
- NSAIDS Non-steroidal anti-inflammatory drugs
- NTDT Non transfusion dependent thalassaemia
- SHT Specialist Haemoglobinopathy Team
- TDT Transfusion dependent thalassaemia
- TRV Tricuspid regurgitant jet velocity
- UKTS United Kingdom Thalassaemia Society
- uPCR Urine protein creatinine ratio
- USS Ultrasonography

Process for monitoring compliance and effectiveness

Monitoring of adherence to this guideline will be the responsibility of the HCC. The HCC and local data management teams will coordinate regular review, collection of 'Dash Board' 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** for details on how to contact*).*

Dissemination and implementation

This guideline replaces all previous guidance for the care and treatment of adult patients with thalassemia. The guidance will be made available via local trusts / hospitals intranet. Managers of local trusts must ensure that all staff working with adult patients living with thalassaemia 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 executive ownership of the guidance sits with the local Medical Director.
- **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 thalassaemia should be signposted to the guidance in this document. 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 thalassaemia 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 thalassaemia 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 June 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 and pregnancy status but these differences are based on national good practice guidance (provision of CMV negative units).

Contact Details

Please refer to **Appendix 2** for details of how to contact the red cell team in and outside of normal working hours. Please refer to **Appendix 4** for details on teams to be referred to. {*Appendix 2 and Appendix 4 must be completed locally – delete this sentence once done}.* LHTs should include how to make contact with SHT / HCC teams to discuss care and transfer if necessary. Local arrangements for referral to other clinical teams (for example obstetric / surgical / urology) must also be included.

GENERAL ASPECTS OF CARE

Acute clinical presentation

People with thalassaemia rarely present to hospital for non-elective care but when they do they may be very sick and need urgent assessment and management. This is particularly of concern in people who have poor iron control either currently or previously; those who have multiple comorbidities and those with significant extramedullary or excessive intramedullary haematopoiesis. On attendance it is essential that the red cell team are informed (see **Appendix 2**). Some problems are common in this group of patients and awareness of these is essential for prompt diagnosis and appropriate treatment. When acutely unwell, thalassaemia patients may tolerate anaemia poorly and require transfusion (see below).
Rapid assessment, prompt treatment and effective monitoring are essential in achieving a successful outcome (**summary** provided in **Appendix 3**).
There are some acute worrying clinical presentations that are more common in thalassemia patients and these include:

- cardiac failure and cardiac arrhythmias often due to current or previous cardiac iron loading
- sepsis (increased likelihood in those with iron loading and splenectomy often with a different profile of organisms)
- VTE, including line-related, atypical site and unprovoked
- osteoporotic fracture
- spinal cord compression after fracture or from extramedullary haematopoiesis
- endocrine dysfunction, including diabetes, thyroid, calcium and adrenal
- gallstones and cholangiopathy
- renal stones, renal colic and urosepsis
- acute chronic liver decompensation: cirrhosis or concurrent viral hepatitis.

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.

Investigations

- FBC
- Renal profile,
- Liver profile
- Bone profile
- CRP
- Group and Antibody Screen (Group and Save / Crossmatch)

If clinically indicated:

- Cultures (blood, urine and / or swab)
- Serum amylase
- Atypical respiratory serology, sputum/throat culture
- Urine for Pneumococcal + Legionella antigen
- Coagulation screen
- CXR
- US abdomen
- CT abdomen and pelvis (CT AP)
- CT Kidneys, ureters and bladder (CT KUB)
- Lumbar puncture
- ECG +/- echocardiography
- BNP and troponin
- CT pulmonary angiogram (CTPA)
- Group and antibody screen +/- DAT

- Malaria screen if recent visit to endemic area
- VBG for blood glucose and blood ketones

Presenting complaint

- History of presenting complaint as outlined by patient or carer.
- Site and severity of any pain.
- What analgesia has been used.
- Any precipitating event, for example diarrhoea, vomiting, infection, stress etc.

Past Medical History

- Hospital patient usually attends for care
- Review patient medical record and record:
    - Thalassaemia genotype / phenotype; whether TDT or NTDT.
    - Treatment regimens, medication and transfusion regimen.
- Date of last transfusion. Transfusion history including alloimmunisation and where else transfused (this information should be explicitly imparted to the transfusion laboratory).
- Complications for example splenectomy, venous thromboembolism, osteoporosis, diabetes, iron overload, gut, cholecystitis.

Examination and investigations

- Patient examination
- Initial investigations in line with local ED protocols for presenting complaint but when reviewing result ensure the date of last transfusion is considered.

Critical warning signs

The commonest causes of death in patients living with thalassaemia are infection, particularly in splenectomised patients, and complications of iron overload such as cardiac arrythmia and liver disease.

Indications for immediate admission:

- **Fever >38° C, tachycardia, tachypnoea, hypotension**
- **Acute abdominal pain or distension**
- **Worsening jaundice (mild/moderate jaundice common in steady state)**
- **Altered consciousness or convulsions**
- **Symptoms or signs of central venous catheter infection**

Management

- Some patients are on long-term prophylactic antibiotics. If unwell a low threshold to commence empiric antibiotic treatment based on local microbiology guidelines is appropriate.
- Some patients are at medium / high risk of VTE ensure local guidance is followed unless contraindicated.
- **Venous access** can be challenging, even blood tests can be extremely 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.
- Patients will be living with chronic pain and discomfort and may be on regular doses of strong analgesics. This needs to be taken into consideration when deciding on the type and dose of pain relief.

Monitoring

- Observations should be performed in line with ED protocols.

Nursing Care

- Ensure physical comfort and provide emotional support.
- Nursing in isolation should be performed in line with local guidelines.
- Ensure observations are performed and recorded in line with ED protocols.
- Ensure red cell team is aware that the patient is in the ED department.

Admission

- Initial triage, assessment and management will be performed by ED or Ambulatory Care where the hospital has this service.
- The admitting team will be under the specialist for the presenting complaint but it is essential to ensure that the haematology red cell team are aware and that the patient is reviewed.

Discharge

When the reason for admission is not directly related to thalassaemia the red cell team should be consulted regarding discharge planning and follow up. Patients who are due for their next routine blood transfusion may benefit from this being performed during the hospital admission. A copy of the discharge summary should be made available to all relevant parties in line with local policy.

Outpatient Management, Annual Review and Elective Surgery

Most adults with thalassaemia will have been identified in childhood and have a confirmed diagnosis and care plan at the point of transfer to the adult service. Occasionally a new patient joins the clinic as they have moved into the area from elsewhere in the UK or from abroad. Where possible they should encouraged to bring records from their previous hospital and an 'annual review' performed so nothing is missed. Patients should be provided with information outlining contact details and services available, including the day unit and psychosocial services available. In addition, patients should be informed about patient support groups, including the UK Thalassaemia Society (UKTS), with relevant with contact details provided. The patient should receive explanation of the National Haemoglobinopathy Registry (NHR) subsequent to the visit the patient should be registered on the NHR or details changed to reflect the new service provider.

a) New patient clinical assessment should include:

- Detailed history: including diagnosis, understanding of diagnosis and symptoms of anaemia; any operations, splenectomy; other history for example thrombosis, fractures, leg ulcers.
- Transfusion history (age at first transfusion, **date and place of most recent transfusion**, usual number of units and interval between transfusions (calculate approximate number of transfusion in lifetime), any antibodies and any adverse effects / events during and following transfusion). This information should be passed onto the blood transfusion laboratory who will need to identify whether a red cell phenotype / genotype is available or samples need to be referred to NHS Blood and Transplant.
- Perceived impact of transfusion, energy levels, back pain, bone pain post and pre transfusion.
- Discussion and documentation of consent for transfusion, in accordance with local policy, outlining the risks and benefits.
- Venous access.
- Vaccination / immunisation history.
- Spleen and liver size.
- Evidence of extramedullary haemopoiesis.
- Iron chelation history, compliance and evidence of iron overload.
- Symptoms and signs of cardiac failure, for example palpitations.

- Menstrual cycle, sexual function, any children with or without assisted conception.
- Full current medication list.
- Family history, siblings, whether bone marrow transplant has been discussed.
- Work / study and social issues.
- Mental health and mental health assessment.

Investigations on new patients will vary depending on the previous treating hospital and the availability of recent and historic results. If the patient has been transfused in the last three months this must be clearly indicated on all request forms and the results reviewed with this in mind. At a minimum consider:

- FBC, reticulocytes and blood film
- G6PD assay (if untransfused)
- Group and antibody screen (may require multiple samples depending on transfusion history).
- HLA typing if not available and patient being considered for stem cell transplant or gene therapy.
- Liver, renal and bone profile, ferritin, glucose, LH and FSH, oestradiol/testosterone, thyroid function, vitamin D, parathyroid hormone, IGF-1, urine protein:creatinine ratio.
- Hepatitis B surface antigen, Hepatitis B surface and core antibody, Hepatitis C antibody, HIV 1 and 2 antibody.
- Urine dip stick, if available.

Where there is no laboratory record of diagnosis the following should be requested to confirm the diagnosis:

- Hb H preparation (if HbH disease suspected).
- Haemoglobin separation by high performance liquid chromatography (HPLC) +/- electrophoresis.
- Genetic analysis for β-thalassaemia mutations and Xmn1 polymorphism (in β-thalassaemias) and α-thalassaemia genotype.

If there is some doubt around diagnosis, then additional genetic or other laboratory tests to define the haemoglobinopathy should be included.

b) Transition from paediatric to adult service within the same service

A care plan should be agreed for all thalassaemia patients before they are transferred from paediatric to adult services; it is essential that this care plan forms part of the patients first appointment within the adult services.

c) Outpatient Management and Annual Review

It is important to acknowledge that these are lifelong expert patients. Outpatient clinic should provide a safe environment to enable difficult discussions about on-going care with familiar staff who patients trust and have sound knowledge and experience.

The aims of outpatient review are to:

- Monitor progress: medical, and psychosocial.
- Establish steady state parameters for comparison in acute illness.
- Educate in the management of thalassaemia and iron chelation in particular.
- Provide counselling and support.
- Check / complete and update the patient's Specialist Patient Care Plan (sPCP). See **Appendix 7** for an example which should be made available for all health care staff to access.
- A patient may wish to discuss holidays and travel arrangements see **Appendix 5.**
- A patient may wish to discuss letters for colleges, employers or applications for support. It is sensible to advise the patient to discuss with the UKTS who have a wealth of knowledge and experience and for annual review and sPCPs to be used to support any applications.

Routine clinic review (approximately every 3 months but variable depending on clinical need and service):

- Document any ill health since last visit.

- Record weight, height (if <21), routine observations (temperature, pulse and BP), review if significant change.
- Examination: check especially for jaundice, heart size and murmurs, liver and spleen size (measure in cm).
- Review laboratory results and request any additional tests (where possible to be done prior to next transfusion unless urgent results required).
- Offer support/referral to Clinical Psychologist where appropriate.
- Medication review (including compliance).
- Arrange follow up or annual review appointment as appropriate.
- Remind patient to make contact if any problems or concerns.

Patients who develop new complications or require significant changes to their management should be referred for discussion at local and / or the HCC network MDT (see **Appendix 9**). If necessary, recommendation will be made at the HCC network MDT for the case to be put to the NHP. Consideration for referral could be significant increase in iron overload, transfusion complications, unexpected acute complications, poor compliance / attendance.

Annual Review Checklist

All patients with thalassaemia should have a comprehensive review on an annual basis at the tertiary centre, details of which are entered onto the NHR by the service data manager (**Appendix 2**). An annual review proforma is provided **Appendix 8** which should be completed systematically. At the end review a comprehensive letter should be prepared and, at a minimum, a copy sent to the patient's GP and to the patient and the annual review proforma sent / available to the red cell data manager. In addition to the proforma the following points should be considered:

- Assessment of progress in general and a review of the patient's knowledge of the condition to include:
    - Education/Employment.
    - Compliance to medication (particularly iron chelation).
    - Discussion about lifestyle including smoking, alcohol, diet, exercise.
- Clinical review
    - Other complications for example venous access / port or line infections .
    - Review of transfusions / annual red cell consumption (calculate mls / Kg red cells transfused) / red cell alloantibodies.
    - Splenectomy may need to be considered in patients with hypersplenism or high red cell requirement defined as >250-275 ml/kg per year of red cells (reference for MDT discussion see **Appendix 9**).
        - Iron chelation review appropriate and sufficient.
- Referral / review to monitor for chronic complications, for example T2*, R2, Ophthalmology, audiology, DEXA.
- Review of laboratory tests
- Discussion regarding the risk and benefits of blood transfusion obtain annual consent in line with consent recommendations (SaBTO, 2020).

d) Management of Elective Surgery

- All patients undergoing surgery should have a clear management plan drawn up by the surgical, anaesthetic and red cell team, documenting the fitness for surgery for the patient with regard to cardiac, endocrine, hepatic and metabolic factors, and the timing of the surgery should be planned and agreed.
- A preoperative assessment should include transfusion history, baseline Hb, an assessment of current iron loading and of iron chelation therapy, current and previous complications relating to iron overload, particularly regarding the potential risk of precipitating or worsening cardiac, endocrine, metabolic and liver dysfunction.

- All patients should have an individualised risk assessment for thrombosis and be appropriately managed to reduce the risk, taking into account splenectomy status, previous history of thrombosis and presence of indwelling intravenous lines.
- Where an acute surgical problem is suspected, medical causes that could explain the presentation should be excluded before surgery
- Blood transfusion support should be planned with the red cell team. The laboratory must be aware of the plan with a full transfusion history if the patient is not known to the facility performing the procedure.
- All patients undergoing splenectomy must be given relevant health education about avoiding/ managing infections and must have recommended antibiotic prophylaxis and vaccinations.

Specific Aspects of Care / Prevention and management of Specific complications

Abdominal and Hepatobillary

There are numerous intraabdominal complications that patients with TDT and NTDT are at greater risk of, these include:

e) Jaundice

If a patient presents with jaundice possible causes include: liver decompensation, cholelithiasis or haemolytic transfusion reaction. Laboratory investigations and history should differentiate which is the cause of the jaundice.

f) Gallstone complications

Gallstone complications are common, with a higher incidence in NTDT than in TDT as regular transfusion suppresses haemolysis. Management should mirror that of the general population, for example CT or ultrasound and MRCP, with early surgical opinion. If biliary tract sepsis is suspected antibiotics should be commenced as per local hospital policy. Complications include:

- Biliary colic
- Cholecystitis
- Ascending cholangitis
- Pancreatitis

g) Infection

Although people with thalassaemia can get the same infections as the general population there are two scenarios which impact them more frequently. Firstly asplenia increases the risk of unencapsulated organisms such as pneumococcus and meningococcus. Patients should be on regular penicillin and have the appropriate vaccinations but concordance and the protection offered by these are not always complete. Iron loading predisposes to certain bacteria such as klebsiella and yersinia enterolitica and patient with iron loading particularly if in the heart, may not be able to tolerate sepsis well. Chelation is usually stopped if sepsis is suspected (please refer to section 13.5).

h) Liver Disease

The two major reasons for liver disease in thalassaemia is iron loading which can cause fibrosis/cirrhosis and hepatocellular carcinoma; and transfusion transmitted infections such as hepatitis B or C. These patient should be managed with support of the SHT and liver team (**Appendix 4**). All patients with **hepatitis** should be under a specialist hepatology service (**Appendix 4**). Patients with chronic viral hepatitis and/or iron overload may present with decompensated liver failure and hepatic encephalopathy. Patients with suspected hepatic decompensation require urgent assessment. Acute hepatic derangement due to viral hepatitis is rare but should be considered if the presentation is with nausea, jaundice and LFTs showing marked transaminitis although biliary problems, chelator toxicity, right sided cardiac failure and portal vein thrombosis should all be considered.

i) Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency is a problem in older patients with thalassaemia properly due to early damage as a consequence of pancreatic iron overload. Abdominal cramps and weight loss are the commonest symptoms. Stool samples should be sent for analysis and blood tests to ensure B12, folate, vitamin D, zinc and magnesium levels are appropriate with replacement given if necessary. Referral to the gastroenterology team is important (**Appendix 4**).

Circulation / Pulmonary / Cardiac

j) Cardiac

Patients with TDT and NTDT can present with cardiac problems independent of their condition however patients with transfusion associated iron overload may present with symptoms of cardiac dysrhythmias or failure which is a medical emergency. Acute arrhythmias need to be managed in conjunction with a cardiologist. Patients presenting with tachycardia, hypotension, pre-syncopal / syncopal episodes and/ or acute cardiac failure should be investigated with a 12 lead ECG in an appropriate area equipped with cardiac monitoring and suitable care. The cardiology and red cell team should urgently discuss best method to rapidly remove iron in patients with myocardial iron overload. If the patient is known to have pulmonary arterial hypertension urgent advice should be sought from the HCC and / or National Haemoglobinopathy Panel (see **Appendix 4** for contact details and **Appendix 9** for MDT proforma).

k) Hypercoagulability and thrombosis

Thromboembolism is a well described complication in thalassemia particularly in those who have had a splenectomy, those with NTDT and those with indwelling CVCs. Optimising both thalassemia and non-thalassemia risk factors is important to prevent and manage VTE.
Thromboprophylaxis should be considered for all patients admitted to hospital as per national guidance (NG and those aged >16 years with CVCs, balancing the patient's individual risk of VTE versus their risk of bleeding. This risk assessment should follow the NICE VTE guidelines (NICE, 2018) noting contraindications or bleeding risks.

l) Leg ulcers

Both TDT and NTDT have a higher incidence of leg ulcers, the pathophysiology remains unclear but may relate to chronic hypoxia, iron overload and a hypercoagulable state as well as increased risk of medical complications which also affect wound healing such as diabetes. Standard wound care principles in line with local tissue viability teams should apply and with the support of the SHT. Referral to specialist dermatology and plastic surgery teams may be appropriate in severe cases (see **Appendix 4**).

m) Pulmonary Hypertension

Pulmonary hypertension (PHT) is prevalent in non-transfused patients (23%), particularly those who have been splenectomised. NTDT patients should have regular echocardiography (minimum of 5-yearly) from 15 years of age. If there is evidence of raised pulmonary artery pressure on echocardiography (TRV > 3.0 m/s or > 2.5 m/s if symptomatic) referral to the National Pulmonary Hypertension Service (see Appendix D for contact details) for further assessment and consideration of right heart catheter studies. If pulmonary hypertension is confirmed regular transfusion should be considered. Patients with TDT rarely develop PHT however PHT should be considered if symptomatic or concerned when patients should have echocardiography and referral. Iatrogenic pulmonary hypertension has been seen in patients with indwelling CVCs due to undiagnosed chronic pulmonary thromboembolism, consideration of anticoagulation should be made in these cases with the SHT.

Dental

Intramedullary expansion causing bony deformities including that of the skull and fractures, should be prevented by timely commencement of an adequate transfusion regimen. Delayed dental development may occur and the teeth may be short and slender. Patients should be encouraged to attend their dental practice for regular check-ups and to ensure good liaison between the dentist and the patients red cell team. Referral to hospital based oral surgery / maxillofacial surgery services may be occasionally required (see **Appendix 4** for referral route). Dental infection should be managed early and aggressively. Patients should have a comprehensive dental assessment prior to starting any bisphosphonate associated with potential development of necrosis of the jaw. For patients having dental surgery under general anaesthetic please refer to the guidance on 'Management of planned surgery'.

Endocrinopathies / Endocrine

Endocrine/skeletal complications in thalassaemia are multifactorial, contributory factors including ineffective erythropoiesis, iron overload and chelation therapy. All patients with TDT and NTDT should have a full endocrine screen annually and where concern, an assessment by a Consultant Endocrinologist (see **Appendix 4**). Routine screening should have led to a diagnosis before acute clinical presentation however, these may present acutely e.g. with diabetes mellitus and, less commonly, adrenal failure, hypoparathyroidism or hypothyroidism. All such patients should be discussed at the earliest opportunity with the local Endocrinology team and the SHT.

- Adults with evidence of hypogonadism should receive hormone replacement therapy, under the guidance of a Consultant Endocrinologist/Reproductive Endocrinologist.
- Patients should be monitored for glucose intolerance. Random glucose every three to four months, and oral glucose tolerance tests annually. Patients with evidence of diabetes should be referred and iron chelation reviewed.
- HbA1c is unreliable in both TDT and NTDT patients, fructosamine levels give a more reliable indication of glycaemia. Of note: HbA1c should be OK in patients with HbH.
- Calcium and phosphate should be measured every 3-6 months. Vitamin D levels and parathyroid hormone should be checked annually and vitamin D / calcium replaced given as necessary.
- Thyroid function should be assessed at least annually, if abnormal and patient is not taking thyroid replacement consider starting via GP surgery.
- Annual monitoring of morning Cortisol
- Bone mineral density in the hip and spine should be measured at least every three years in TDT more frequently if there is concern, by dual energy X-ray (DEXA scan). Patients with osteopenia (T score between -1 and -2.5 in either hip or spine) or osteoporosis (T score < –2.5) should be managed with advice about diet, exercise, calcium and vitamin D supplementation and possible hormone replacement therapy. In established osteoporosis bisphosphonate therapy should be considered on Consultant Endocrinologist / metabolic bone service advice.
- For management of NTDT patients with significant iron overload at risk of endocrinopathy see section above on Endocrine/Skeletal complications in thalassaemia major. NTDT patients are at increased risk of osteoporosis. Management should follow the guidance above with the exception that in milder phenotypes without other risk factors e.g. iron overload DEXA scan can be repeated 5-yearly if bone mineral density is normal. All patients should have an annual review including the assessment of facial bone deformity.

Infection

Patients with thalassaemia are more vulnerable to infection including gram-negative sepsis. Splenectomised patients, who should be on prophylaxis (penicillin V 250mg po bd or erythromycin 500mg po bd) are at risk of overwhelming infection. **Prompt** treatment of severe sepsis saves lives. Implementation of 'Sepsis Six' (oxygen, cultures, antibiotics, fluids, lactate measurement and urine output monitoring), along with local infection policy should be followed for choice of antibiotics, dosing and monitoring guidance. Appropriate investigations (e.g. blood, urine cultures) should be taken prior to giving first dose of antibiotics, but this should not delay generic therapy. If unsure or the patient is known

to be penicillin allergic discuss with Microbiology team (see **Appendix 4**). Most common sites of infections

include the chest, biliary tree and soft tissue. Indwelling CVCs should also be considered. The organisms most often isolated are Klebsiella pneumoniae, Escherichia coli, Streptococcus pneumoniae, Salmonella typhi and Yersinia enterocolitica. The pathogenicity of these organisms is increased in the presence of iron overload. Of note:

- Patients with thalassaemia are more susceptible to infection with ***Yersinia enterocolitica*** which thrives in an iron-rich environment. This diagnosis should be suspected in any regularly transfused patient with fever, diarrhoea and abdominal pain.
- **Parvovirus B19** can cause a temporary red cell aplasia resulting in severe anaemia. In patients with a haemoglobinopathy presenting with an acute anaemia and viral prodrome, a reticulocyte count and parvovirus serology should be sent to the laboratory and the patient should be transfused if needed. Family members particularly those also with haemoglobinopathies should be screened for infection and have an FBC check.
- **Patients on deferiprone** are at risk of agranulocytosis or neutropenia and should have an urgent full blood count every time they present with an acute problem to the hospital or GP. If T>38.0°C for 2 readings 1h apart, or a single reading >38.5°C and neutrophil count < $1x10^9$/l then antibiotics should be instituted as per the febrile neutropenia policy, treatment with deferiprone discontinued immediately and G-CSF administered.
- **Patients on deferasirox**: Certain organisms utilise Deferasirox as a siderophore as a and their pathogenicity is increased, so it should be temporarily withheld in patients presenting with an acute infection.

Mental Health / Psychological Care

Living with thalassaemia is a significant commitment to both the individual and their family. Regular blood transfusion, time off school and work, adherence to chelation and understandable anxieties and concerns regarding their health can weigh heavily. Those with comorbidities may have the added stress of multiple additional appointments, medications and concerns regarding fertility and longevity.
There is a variety of psychological support available to patients locally or via the HCC (**Appendix 4**) with dedicated clinical psychologists trained to assist in the management of emotional concerns in relation to physical health problems. Access to specialist psychological support around how to engage and comply to difficult and challenging prevention and treatment protocols is essential. 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 all health care providers. At a minimum all patients 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 3** and **Appendix 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.

Neurological

Patients with thalassemia even well transfused can develop bone marrow tissue masses outside the confines of the bones (extramedullary haematopoiesis). Commonly along the paravertebral gutter or pre sacral but occasionally growth can be within the spinal canal and can cause spinal cord compression. If patient complains of unusual sensation in the limbs, difficulty with bladder or bowel sensations, new

pains in lower limbs a full neurological examination and if abnormal findings request an urgent MR scan. If

identified management may be with hypertranfusion, hydroxycarbamide, local radiotherapy or a combination of these.

Ophthalmology / Ocular Complications

Ophthalmic changes may be due to the disease, iron overload or iron chelation therapy. Ocular toxicity with desferrioxamine (Desferal®) is well documented in patients treated with high doses usually presenting with blurred vision or colour impairment due to metals (copper and zinc) essential for normal retinal function being removed. Patients on desferrioxamine (Desferal®) should yearly monitoring with ERG and ophthalmological examination. Patients on lower doses of desferrioxamine (Desferal®) and those on deferasirox (Exjade®) should have baseline assessment and urgent referral if visual disturbances are reported (see **Appendix 4** for referral details).

Orthopaedic Complications

Patients with thalassemia are at increased risk of developing osteoporosis putting them at risk of needing elective or urgent surgery. Where the patient presents acutely the admitting team must inform the red cell team of the admission. For elective surgery see the section on 'Management of Elective Surgery' and see **Appendix 4** for who to refer to. An MDT should be arranged with both orthopaedic and red cell team to ensure preoperative assessment and timings of transfusion are planned.

Pain management

Many older patients living with thalassaemia experience chronic and chronic on acute pain. Studies show pain is often unreported and self-treated. It is important to discuss pain in outpatient review and to consider good effective and safe treatments. Patients with high analgesic requirements should be considered for MDT and referral to the complex pain team or other relevant services.

Renal and urological complications

Renal calculi are recognised complication, particularly in older patients, and are in part due to hypercalcuria. Unexplained abdominal, flank and back pain and/or a decline in renal function should prompt a CT or ultrasound imaging, early urological opinion and if urinary tract sepsis is suspected antibiotics should be commenced as per local hospital policy. Complications of renal stones include:

- Renal colic
- Obstructive nephropathy
- Super added renal tract infection, recurrent infections should prompt consideration of prophylactic antibiotics.

Iron chelation and the impact of anaemia may cause underlying renal dysfunction. The iron chelation itself can also cause renal dysfunction particularly the use of the chelator Deferasirox. Renal function should be monitored monthly whilst on Deferasirox and input from a specialist renal team should be sought if it does not resolve following dose reduction or cessation. Furthermore, if there is an unexplained electrolyte disturbance, urinary electrolytes should be checked and advice sought from a specialist renal team as this may represent a renal tubulopathy (see **Appendix 4** for referral).

Sexual Health / Obstetrics / Gynaecology / Fertility

n) Fertility

Patients of reproductive age should have received information on contraception and the importance of partner testing and optimising health and iron loading prior to planning pregnancy. Intentions regarding pregnancy should be discussed at the annual review. Testing of haemoglobinopathy status of partners should be offered. If the couple is at risk of having a child with a major haemoglobinopathy they can be offered genetic counselling including the option antenatal diagnosis and where possible, pre implantation genetic diagnosis (see **Appendix 2** community counselling service). Where egg and / or sperm donors are being considered it is important that the couple request screened for haemoglobinopathies of the

donor. Referral for problems with fertility should be to teams with specialist knowledge of red cell disorders (see **Appendix 4**).

o) Obstetrics and gynaecology

Despite the reduced fertility associated with thalassaemia women should be advised to use contraception until such a point that pregnancy is desired. Family planning should be part of each annual review with discussions around risks and ensuring optimisation of iron levels prior to pregnancy. It is sensible to ensure baseline DEXA, T2* MRI, R2 MRI, ECG, echocardiogram and glucose tolerance results are available.

Women with thalassaemia should be managed antenatally jointly by the specialist haemoglobinopathy team and an obstetrician who specialises in haemoglobinopathy (**Appendix 4**).

- **Pre pregnancy medication:**
  - Folic acid 5mg/day should be started 3 months prior to conception.
  - Prophylactic penicillin V 250mg twice daily if splenectomised
  - Oral iron chelation should be reviewed and deferasirox and deferiprone stopped ideally 12 weeks prior to any planned fertility treatment or attempting natural conception.
  - Desferrioxamine can be continued up to the day of ovulation for assisted conception or as soon as a period is missed and pregnancy test is positive in natural conception.
  - If ACE inhibitors are required to improve cardiac function, or intensive iron chelation necessary to reduce cardiac iron, conception should be postponed until these can be safely stopped or converted to alternative drugs that are safe in pregnancy.
  - Vitamin D levels should be optimal
- **During pregnancy, delivery and post-natal**
  - The pregnancy should be managed by the specialist obstetrician with input and advice from the red cell team.
  - It is sensible to have regular MDTs to discuss, issues, problems and any plan particularly regarding the mode and date of delivery.
  - VTE risk should be assessed in an individual basis in line with local protocols, women with thalassaemia should be considered as being at high risk.
  - Post delivery there should be review by the red cell team prior to discharge with discussion about which medications to restart particularly with regard to iron chelation.
  - It is not mandatory but consider coordinating blood tests, blood transfusion and outpatient visits as their appointment load while pregnancy is high.
  - Women with both thalassaemia and diabetes should have monthly assessment of serum fructosamine concentrations and review in the obstetric diabetic clinic.
  - Blood Transfusions: the guidance on blood transfusion is the same as in Section X but transfusion volumes or intervals between transfusion may change depending on the pre transfusion Hb level aiming for a pre transfusion haemoglobin of 100 g/l. Women with NTDT who are asymptomatic with normal fetal growth and low haemoglobin should have a formal plan outlined in the notes with regard to blood transfusion in late pregnancy.
  - Women with myocardial iron loading who are continuing with pregnancy should be monitored closely with a plan discussed and agreed via an MDT HCC meeting.
  - Women with severe hepatic iron loading who are continuing with pregnancy should be carefully reviewed with a plan discussed and agreed via an MDT HCC meeting.
  - Breastfeeding is safe and should be encouraged.
  - Contraception advise should be given prior to discharge

Treatments

p) Blood transfusion

The reader must comply to all the requirements of local blood transfusion policy.

The recommended treatment for TDT is lifelong regular blood transfusion enabling normal growth and physical activity while limiting iron and circulatory overload. Blood transfusion is usually initiated in

childhood based on the severity of the anaemia and the molecular diagnosis. The timing and interval between transfusions is multifactorial and the patient's lifestyle (work / education and other commitments) must be considered. To ensure compliance and to reduce anxiety and stress treatment plans must be agreed with and approved by the patient. The aim is for a pre-transfusion Hb level of 95 – 105 g/L; higher (110 – 120 g/L) may be required in patients with cardiac impairment or significant extramedullary haematopoiesis; aiming to achieve a post transfusion Hb of approximately 140 g/L. Most adults require 2 or 3 red cell units every 3 to 4 weeks. As a general guide, transfusing a volume of 4ml/kg will typically give an increment in Hb of 10g/L.

The individual transfusion plan must be reviewed / discussed with a red cell team Consultant at least annually at the annual review or sooner if there is notable change such as a new alloantibody, a significant transfusion reaction or if the pre-transfusion Hb is persistently below 90 g/L, when the volume of blood received and / or the transfusion interval with each should be reviewed and an adjustment made.

Patients who are not transfusion-dependent (NTDT) may present with an acute fall in Hb from their steady state. In these circumstances a single transfusion may be given in the first instance. If the Hb subsequently falls and no reversible cause, e.g. intercurrent infection is identified, long-term transfusion may be indicated. NTDT Sporadic transfusions should be considered for episodes of acute anaemia, for example precipitated by infection. Long-term transfusion may be considered in NTDT for the following indications:

- Symptomatic anaemia
- Delayed puberty
- Skeletal abnormalities e.g. facial deformities, recurrent fractures, premature epiphyseal fusion
- Pulmonary hypertension,
- Compression syndromes due to extramedullary haemopoiesis
- Chronic leg ulcers

The patient should be observed closely over several months to determine steady-state symptoms and Hb before a decision on long-term transfusion is reached. The rationale for transfusion should be carefully explained if necessary over the course of several clinic visits and should always involve the patient's primary Consultant at the tertiary centre.

The risks associated with regular transfusion include acute and delayed transfusion reactions, allo-immunisation, transmission of bacterial / viral infections and, in the long-term, iron overload (refer to the local Blood Transfusion Protocol for management of reactions). Serious hazards are rare and minimized by meticulous attention to protocols in transfusion practice. SaBTO (Advisory Committee for the Safety of Blood Tissues and Organs) recommends at least annual discussion about the risks of transfusion at least annually (SaBTO 2015). Any changes in risk (for example a new blood borne virus or a new test / treatment to make transfusion safer) should be explained to the patient and written information provided. It is recommended that annual consent is documented as part of the annual review visit

Pre-transfusion testing

All patients should have a local ABO and Rh and K group. In addition all patients should have a red blood cell genotype on record via the national laboratory. Usually, a pre transfusion sample is required within 72 hours of the planned transfusion but this can be extended to 7 days for certain regularly transfused patients.

Administration of blood

Administration and monitoring must be in accordance with local policy. Transfusion is usually administered via a peripheral venous cannula or indwelling intravenous device in a day unit setting (see **Appendix 2** for information). For patients living with thalassaemia blood transfusion therapy is lifelong; maintaining good and adequate venous access is essential along with a good trust relationship with health care professionals administering their care. No more than two attempts at cannulation should be made by an individual practitioner, unless the patient agrees to further attempts. If initial attempts fail a more experienced practitioner should attempt cannulation. Hospitals should have the capacity to use devices such as ultrasound cannulation for those who are difficult to cannulate. The patient may often be

helpful in advising where their accessible veins lie. In adult patients in steady state with normal cardiac function transfusion, with adequate monitoring in line with BSH guidance (Robinson 2017), administration rate of

90 minutes per unit is often tolerated, though there is evidence that such patients may tolerate a rate of an hour per unit (Sinclair 2013). Slower rates of 2-3 hours per unit are recommended in all other patients including those who have not tolerated faster rates.

q) Cellular therapies

Gene therapy, namely technology harnessing CRISPR-CAS-9 to turn on foetal haemoglobin production has now been MHRA approved in the UK for patients with transfusion dependent thalassemia and NICE approval has been sought. Once NICE approval is forthcoming, there will be a clear policy regarding transplant work-up and consent and it is likely that patients eligible for this treatment will require NHP approval. (**Appendix 9**).

r) Extramedullary haemopoiesis

Patients presenting with symptoms due to extramedullary haemopoietic masses should be investigated, usually with MRI imaging, and treated with one or a combination of; hypertransfusion, hydroxycarbamide and/ or radiotherapy. Radiotherapy is often considered if there is urgent need for regression, depending on the site, for example, if impinging on the spinal cord. as hypertransfusion and hydroxycarbamide act more slowly. The patient should be discussed at the SHT MDT for a decision regarding the best treatment (**Appendix 9**).

s) Hydroxycarbamide

Responses to hydroxycarbamide in NTDT are variable, but it may be considered for alleviation of symptoms of anaemia, reduction in jaundice due to haemolysis, relief of bone pain, reduction in medullary expansion or splenic enlargement and regression of extramedullary masses. Hydroxycarbamide therapy is more effective in specific genotypes including HbE/β-thalassaemia, Haemoglobin Lepore/β- thalassaemia and patients who are homozygous for the Xmn1 polymorphism or have been splenectomised. It is not indicated in haemoglobin H disease. Hydroxycarbamide should be started at a dose of 10 -15 mg/kg/day, and the full blood count monitored weekly for the first month, then four to six weekly. The maximal dose is unlikely to exceed 20 - 25 mg/kg/day as the risk of bone marrow suppression is greater than in sickle cell disease. Patients from countries where transfusion is not readily available may arrive in the UK on treatment. Guidance on counselling before and monitoring hydroxycarbamide therapy is provided in the Guideline Sickle Cell Disease - Clinical Management in Adults. A patient information leaflet is provided in **Appendix 6**.

t) Iron chelation

There is approximately 200 mg of iron in every red cell unit transfused and unlike in health ineffective haemopoiesis means that iron stores are not used up leading to iron overload. If untreated iron overload in TDT is usually fatal but even with treatment can cause significant morbidity, therefore careful monitoring is paramount. The majority of deaths are due to iron related cardiomyopathy, presenting as cardiac arrhythmias and cardiac failure. In addition, to cardiac damage, iron toxicity causes hypothalamic and pituitary damage resulting in growth, hormone and gonadotrophin deficiency, short stature, delayed or absent puberty, infertility, endocrinopathies include glucose intolerance, diabetes mellitus, hypothyroidism and hypoparathyroidism. The liver is also an important target of iron toxicity: hepatic fibrosis can develop from an early age eventually leading to cirrhosis, liver failure and hepatocellular carcinoma. Hepatic complications are accelerated in the presence of chronic hepatitis C virus infection. The aim of chelation should be to achieve a ferritin 500 – 1000 µg/L; T2* values >20 ms and LIC of 3-7 mg/g dry weight. Figures under these values carry a risk of medication toxicity and persistently higher significant organ morbidity or mortality.

The most common barrier to effective iron chelation is inadequate compliance. This should be checked and discussed at every visit. There are many reasons for poor or erratic adherence including psychosocial factors. It is important to identify these and offer support through the multidisciplinary team. New team members should be offered specialised teaching on the use of iron

chelators along with barriers to treatments. Any patients of concern or where there is need for significant changes in chelation treatment

should be discussed via an HCC MDT and taken to the NHP if required (see **Appendix 4**). **If a patient is acutely unwell for reasons unrelated to iron overload it is sensible to suspend chelation therapy until the red cell consultant can review.**

Current Iron chelators

There are 3 drugs available with specific indications and licence (NHSE 2022)- deferasirox (Exjade®), desferrioxamine (Desferal®) and deferiprone (Lipomed®). Used as single agents or in combination. Readers should refer to BNF and BSH guidance (Shah, 2021) on use prescribing and monitoring.

Indications for starting chelation therapy

In the majority of cases iron chelation will have been initiated by the paediatric services and as such it should be part of the patients transition care plan to the adult service. Traditionally iron chelation therapy was initiated by 10 - 12 transfusions (>20 red cell units) and/or when the serum ferritin level was consistently greater than 1000 µg/L. However, it is often the case in childhood that chelation is started earlier with a low dose with gentle incrementation. The aim of chelation therapy is prevention NOT rescue.

Monitoring of iron load

Serum ferritin. Serum ferritin is an acute phase protein and values should be correlated with the clinical status of the patient and CRP. Aim to maintain ferritin at 500-1500 µg/L.

Cardiac and hepatic T2* MRI: Gradient-echo T2* sequences are highly sensitive to magnetic properties of tissue iron. This technique provides accurate quantitation of cardiac iron load and function. The risk of impaired left ventricular function increases at T2* values < 20 ms. Nearly all patients with clinical evidence of cardiac failure have a T2* < 10 ms. Any patient with worsening T2* results should be discussed via an SHT MDT (see **Appendix 4**).

FerriScan® R2 MRI: Provides non-invasive quantitation of liver iron concentration (LIC). Ideally patients should be referred for dual analysis of cardiac T2* and FerriScan (R2) at the same visit. A LIC < 1.8 mg/g dry weight is normal. Levels of up to 7 mg/g dry weight do not usually result in organ damage or endocrinopathy. A LIC >15 mg/g dry weight is associated with an increased risk and the results should be discussed via an HCC MDT (see **Appendix 4**).

Summary for monitoring of iron overload

	AIM	TDT	NTDT
Serum ferritin	500 – 1000 ug/L	3 monthly	6 monthly
Cardiac T2* MRI	T2* > 20ms	Annually (2 yrs if good compliance and no previous cardiac iron overload)	If ferritin > 1500 ug/L
		6 monthly if cardiac T2* < 10ms	
		3 monthly if cardiac T2* < 10ms and evidence of cardiac impairment	
FerriScan	LIC <7 mg/g dry weight	Annually	If ferritin > 1500 ug/l
		6 monthly if LIC > 10 mg/g dry weight or change in treatment	

Chelation for NTDT patients can be less intense than in thalassaemia major. Serum ferritin is a useful monitoring tool but can be unreliable in patients with high inflammatory markers and can be less reliable in NTDT and tends to underestimate the degree of liver iron loading. Iron-related cardiomyopathy is

unusual in children and young adults but may develop later in adult life even in untransfused patients. All patients with NTDT should have cardiac T2* MRI and LIC quantitation by FerriScan (R2 MRI) at least

every 5 years or annually if on regular transfusions. These will be arranged at the tertiary centre. Chelation regimes for untransfused patients can be less intensive than in thalassaemia major. Negative iron balance is more easily achieved because the rate of iron accumulation from intestinal absorption is less than that due to regular transfusion.

u) Splenectomy

Patients on adequate transfusion programmes should not develop clinically important splenomegaly. As the spleen size enlarges and more aggressive trnasufsion regimen can halt spleen growth and even reduce the size. Splenectomy is still occasionally performed, however, there is an immediate perioperative risk as well as a longer term risk of portal hypertension, thrombosis and infection. Splenectomy may be considered for patients with: hypersplenism resulting in clinically important leucopoenia, thrombocytopenia, bleeding, symptomatic anaemia or massive splenomegaly with clinical symptoms. Previously splenectomy was recommended in order to increase haemoglobin levels and avoid regular transfusion. However, splenectomy does not provide a permanent alternative to transfusion in these patients and may increase the risk of long-term complications such as thromboembolic disease and pulmonary hypertension. Any patient considered for splenectomy should be discussed at the HCC and / or NHP MDT (see **Appendix 9**). Prior to splenectomy patients should have the appropriate vaccinations (REF green book) and where possible be hyper-transfused for several months to reduce the spleen size, suppress ineffective erythropoiesis and reduce the numbers of circulating, prothrombotic thalassaemic cells. The feasibility of laparoscopic splenectomy should be discussed with the surgical team and an HDU/ICU bed booked for post-operative observation. If the patient has not undergone prior cholecystectomy ultrasound examination should be performed before a date for surgery is scheduled and if gallstones are present cholecystectomy considered at the same time.

v) Stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) can offer a cure for thalassaemia with long term transfusion independence and avoidance of iron chelation. Patients and their full siblings should be offered HLA typing. This should be discussed with the families of children and adults with thalassemia as a treatment option please refer to the NHSE Policy on stem cell transplant in thalassaemia (NHSE 2023). Any suitable patients should be discussed at HCC MDT and if agreed referred to the NHP (**Appendix 9**).

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
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 in line with national recommendations.

Appendix 2. Contact Details of the Red Cell Team

Contact Details of Red Cell Team

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	
Paediatric SpR via Alertive	*24h*

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 Red Cell Team	
On Call Paediatric SpR	*24h - Alertive*
Pharmacy	
Reception	*5401/5402 – normal working hours On Call Pharmacist out of hours*

Other key contacts:		
Day Unit facility for transfusion: AMDU	*12h/day 7 days/week*	*x7442*
Venous access	*IRU x3114*	*Out of hours On call Anaesthetist*
Blood Transfusion Laboratory	*In hours 2906*	*Out of hours 2906*
HDU / ICU admission	*ITU SpR/Consultant on call*	*ITU SpR/Consultant on call*
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*

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 and Essential Care

Acute Management Essential Care

Appendix 4: Referrals to other specialities

REFERRALS TO OTHER SPECIALITIES

It is essential that referrals are made to teams with knowledge and experience in the treatment of patients living with thalassaemia. The table below summarises local arrangements for referral to other specialties for recognised complications of Thalassaemia. Medical complications and problems unrelated to Thalassaemia 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. If possible transfusion iron overload arrange liver R2 MRI if not available.	Evidence of hepatopathy, cirrhosis, unexplained hepatomegaly. R2 LIC > 15 mg Fe/g dw)	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 / liver team *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*) if not available.	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 *Via Red Cell 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*
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	Abnormal findings or concerns	Referral to endocrinology *Outpatient referral or Endocrine SpR on call via Alertive*
	Bone mineral density scan (DEXA)		*Request on ICE*
Infection			
Infection	Fever, rigors, MS&C, treat	Discuss with microbiology if unresolved or problematic.	Referral to Consultant Microbiologist *x4587*
Mental Health			
Mental health	Discuss in outpatient clinic and ensure mood score at least annually.	Referral if indicated and patient consents.	Referral to red cell psychology service *Community Mental Health team referral*
Ophthalmology			
Retinopathy	Screen in accordance with iron chelator guidance.	Routine screen.	Ophthalmology *Outpatient referral*
Orthopaedic			
Orthopaedic problems			Orthopaedic service *Outpatient referral or inpatients via Orthopaedic SpR on Alertive*
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 increasing medication, opioids.	Referral to Red Cell Psychologist for help with non-pharmacological interventions. Referral to MDT chronic pain team might be beneficial eg local nerve block etc	Referral to psychology service 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)			
Fertility	Encourage partner testing Usually refer patient to GP	Referral to specialist counsellors if potential of TDT 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. Consider HLA typing patient and family members.	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*
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			*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 *Usual care team will discuss at Red Cell MDT*

Appendix 5: Traveling / Flying and Thalassemia

Information for patients
The main problems with travel in patients living with thalassaemia is the restrictive nature of their transfusion regimen. Most patients will arrange holidays in the mid two / three weeks in between their planned transfusion dates; occasionally, if going abroad for longer, they may organise a transfusion in the country visited. It is essential for all to be adaptive to the needs of the patient and the family while ensuring good communication and exchange of information.

Example of a travel letter for the patient to carry with them:

Red Cell Team Clinical Haematology

TO WHOM IT MAY CONCERN

Re : *{INSERT PATIENT'S DETAILS}*

The above named is under the care of the red cell services for thalassaemia (*insert genotype*). Thalassaemia is an inherited condition requiring life long blood transfusion support. For this reason he/she carries a small supply of 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.
The patient has been optimised for travel, receiving a blood transfusion on (*insert date of last transfusion*). Should any further information be required please contact (*insert name and contact details*)

Yours faithfully

{Name; position and hospital}
{Contact details}

It would be sensible for the patient to carry a copy of their last annual review letter, contact numbers and any specific transfusion requirements just in case they require transfusion or treatment while abroad. They should be reminded to inform the local team on their return of any transfusions or treatments received.

Appendix 6: Hydroxycarbamide (Hydroxyurea) Information Sheet (occasional use in NTDT)

Introduction

In the UK, it is recommended hydroxycarbamide is offered to EVERYONE with HbSS, or Hb Sβ^0 thalassaemia. This is based on the evidence of improved life expectancy, reduced sickle damage to organs, reduction in frequency and severity of pain crises, and less need for blood transfusion. 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 to increasing HbF 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 improvement with both fewer and less severe painful crises. In addition the study showed, in the prolonged follow up, 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 or thalassaemia for example HbSC, Hb Sβ^+, NTDT 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 but there is also a lot of research into its use for people with sickle cell disorders.

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 team. 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 a degree of 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 7 Example of Specialist Patient Care Plan

ADULT THALASSAEMIA: 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* **Beta Thalassemia Major / TDT; Beta Thalassamia Intermedia NTDT**		
Allergies: **NKDA** *OR delete and insert any allergies*		
Treatment Regimen		
Insert usual transfusion regimen (eg 3 units every 4 weeks) *Insert iron chelation regimen* *Blood Group and antibody status* *Previous adverse events* *Medication routinely given with transfusion*		
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: • *Diabetis* • *Osteoporosis* • *Iron overload* For more information please refer to the patient's last comprehensive out patient annual review.		
Routine Medicaiton		
Addition Information		

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

The Red Cell Network
Haemoglobinopathy Coordinating Centre

Appendix 8 Example of data required for comprehensive annual review.

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					
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	*BMT, Hydroxycarbamide*				
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)		
Endocrine review		
Ophthalmology assessment		

Specialist Imaging Type	Date	Result
Ferriscan Liver Iron (mg/g/w)		
MRI Hip / Shoulder (AVN)		
DEXA Bone Scan		
Other:		

Blood Tests: (Pre transfusion in TDT; date of last transfusion NTDT.....)

Hb		Bilirubin umol/l		HbF% (if applicable)	
		ALT u/l			
Neutrophils x 10^9/l		Creatinine		Ferritin	
Platelets x 10^9/l		Vitamin D		Transferrin saturation %	
		LDH		Iron	
		Urine PCR			
		TFT			
HCV		eGFR			
HBV					
HIV					
HBsAb					

Enter any other blood test results required in spaces.

Current issues:

Discussion and actions:

Completed by:.....**Date:**

Appendix 9: Example of MDT proforma

HAEMOGLOBINOPATHY MDT PROFORMA			
MDT date		Patient name	
Referral hospital		Hospital No.	
Referral Consultant		NHS No.	
MDT Number (Admin use only) New patient or Follow up (delete)		DOB / Age	
		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