Introduction and Who Guideline applies to

This document briefly describes management of thalassaemia with specific reference to:

a) Routine care management, including monitoring requirements

b) Iron chelation therapy

c) Management of complications in patients with transfusion dependent thalassaemia

- Chronic complications
- Acute complications
- Special Circumstances

d) Management of non-transfusion dependent thalassaemia

This guideline is for use by any member of staff involved in the care of a patient with thalassaemia.

Guideline Standards and Procedures

Thalassaemia is a condition where there is a quantitative defect in haemoglobin production. This can either lead to transfusion dependence (thalassaemia major) or non-transfusion dependence (thalassaemia intermedia). All patients will be offered an annual review in the haemoglobinopathy clinic and will be registered onto the National Haemoglobinopathy Registry (NHR).

As a specialist haemoglobinopathy team, UHL has overall responsibility for these patients. As the regional Thalassaemia Haemoglobinopathy Coordinating Centre (HCC), Sandwell and West Birmingham NHS Trust will also be involved in their care. Complex cases should be referred to the regional MDT to reflect this.

Transfusion Dependent Thalassaemia

This is an autosomal recessive condition characterised by the production of no or very little B globin chains leading to little or no Haemoglobin A production. Haemoglobin A is the major haemoglobin component over 1 year of age (accounting for over 90% of haemoglobin (Hb)) so a reduction means that the individual is severely anaemic from approximately one year of age. If untreated this leads to profound failure to thrive and death in childhood.

Red cell transfusion therapy is the mainstay of treatment so the major issues faced by this group of patients are now long term consequences of red cell transfusion therapy including infection, formation of antibodies, reactions to blood but mainly iron overload. The major focus of treatment is to manage the consequences of continuing transfusion and allow normal life with minimal disruption.

Aims of transfusion:

- Maintain pre transfusion Hb 90-105g/L (usually given every 2-4 weeks). Patients with extramedullary haematopoiesis (EMH), cardiac disease and/or inadequate bone marrow suppression may require higher transfusion targets.
- Transfuse ABO, Rh, Kell matched blood which is fresh as possible with a sample obtained within 72 hours of transfusion episode.
- Timing of venepuncture and transfusion should aim to minimise disruption to the patient's life. A maximum of 3 attempts at cannulation by each individual, although practitioners are advised to get a colleague to take over if cannulation is difficult. Waiting times should be kept to a minimum and certainly within 30 minutes.
- Out of hours transfusion is provided on a Saturday.
- The volume of blood to transfuse should be calculated by the following formula:

  $$\text{Volume to transfuse (ml)} = \frac{\text{Desired Hb (g/l)} - \text{actual Hb (g/l)}}{\text{weight (kg)} \times 4} \times 10$$

- To reduce donor exposure, transfusion requirements should be rounded to the nearest whole unit.
- All blood should be given in line with UHL transfusion policy and can be authorised by a non-medical prescriber who has undergone sufficient training and deemed as competent to do so.

Anaemia impact monitoring

- This is difficult in adults as growth has usually been completed
- Features of back pain or bone pain towards the end of the transfusion cycle may be an early feature
- Evidence of hypersplenism can develop following prolonged periods of chronic under transfusion. (low wbc and platelet count associated with high annual transfusion requirement but low pre-transfusion Hb). Patients with pain symptoms in the spine should be offered MRI assessment to look for evidence of spinal deformities due to EMH.

Iron Overload (IOL):

- This is primarily secondary to transfusion in TDT patients. It can occur in NTDT patients due to increased GI absorption.
- This can lead to accumulation in the heart leading to cardiac failure, as well as liver cirrhosis and endocrinopathy.
- Importance on monitoring as outlined below.
- Ferritin is an indirect measure of iron burden and there can be significant variability. Trends can be helpful, especially as iron levels fall but should not be used to introduce/significantly change chelation dosing without additional monitoring with LIC/T2* MRI.
- Rate of iron loading (ROIL) from transfusion can be calculated to review required chelation doses.

ROIL = units of blood transfused x200 / Weight x days over which blood administered

Monitoring requirements for transfusion dependent patients	
Monthly (**only** if on Deferasirox)	U&E LFT Urinalysis
3 monthly	Ferritin Fructosamine (if diabetic)
Annually	Urine: ACR (if diabetic), U&E/LFT (if on deferasirox) Vitamin D, Bone profile +/- PTH (if low calcium) Oral glucose tolerance test TFT/LH/FSH +/- oestradiol or testosterone Ferriscan MRI (or other liver iron monitoring) • Repeat at 6 months if rapid fall in LIC, LIC <3mg/g/dw or >15mg/g/dw Ophthalmology and audiometry Calculate transfusional iron loading

Others	Cardiac T2*: baseline and monitoring as follows: a. Every 2 years if stable ferritin and previous T2* >20ms b. Repeat at any time if LIC >15mg/g/dw c. Repeat annually if previous cardiac iron but compliant with chelation and level 10-20ms d. 6 monthly if T2* <10ms Echocardiogram: every 2 years unless previously abnormal or new symptoms 24 hour ECG if relevant symptoms, irrespective of cardiac iron history DEXA: every 3 years unless otherwise recommended Hepatocellular carcinoma monitoring: USS and AFP blood test every 6 months if history of severe iron loading, previous history of Hepatitis C or known cirrhosis

Outpatient clinic review and monitoring:

Routine clinic review

- Should coincide where possible with transfusion episodes.
- Should include investigations in line with the annual review requirements.
- Clinical examination at least yearly (to include heart/respiratory/abdominal examination, weight, blood pressure).
- Chelation therapy should be managed as per guideline and monitoring arrangements checked (see below).
- Annual review includes summary of treatment based on current national standards (see appendix 1 for proforma). An annual review should be copied to the patient and to SWBH team for documentation.
- All patients require registration on the NHR, which should be updated with each annual review and any significant adverse effects.
- Iron Chelation should be reviewed at least 3 monthly and managed in line with chelation guidance below. The aim of chelation is to limit iron loading in the heart and liver, as guided by ferritin and MRI T2* and Ferriscan (or other mode of measuring liver iron).

New patient to the service

- Detailed enquiry about previous transfusion regime, chelation regime (including side effects) and previous surgery (splenectomy, cholecystectomy).
- Cardiac, endocrine and liver review.
- Discussion of contraception/ fertility/ testing other family members as appropriate.
- Team members (including psychologist) should be introduced, contact numbers given and plan made for routine transfusion support.
- Register on National Haemoglobinopathy Registry (consent for non-research activity no longer required).
- Chelation therapy should be arranged according to previous treatment, current iron loading and patient's wishes. If desferrioxamine to be given contact home care liaison pharmacist.
- Early review should be undertaken to check chelation and transfusion regime working well and to discuss any problems
- If not previously tested, patients should also undergo globin genotyping (α and βglobin genotyping, XMN1 polymorphism)
- Initiate annual review process and review required monitoring as per AR proforma

Iron Chelation Therapy (ICT)

The aims of ICT are to:

1. Maintain safe levels of total body iron to avoid/minimise associated complications
2. Avoid/minimise toxicities of iron chelation therapy

There are three chelating agents which can be used for treatment of iron overload in thalassemia major. These are outlined in the table below:

Adapted from 3rd edition of UK standards	**Desferrioxamine (Desferal®, DFO)**	**Deferriprone (Ferriprox®, DFP)**	**Deferasirox (Exjade®, DFX)**
Route	s.c or i.v injection	Oral (tablet or liquid) Tablet doses: 500mg, 1000mg	Oral (film coated tablet) Film coated tablet doses: 90mg, 180mg, 360mg
Dosage	20-60mg/kg 3-7 times per week	75-100mg/kg/day	7-21mg/kg/day

Considerations	Intensification with continuous IV dosing can reverse cardiac dysfunction Oral ascorbic acid can increase efficacy, but should not be given in early stages of intensive chelation or if T2* <10ms	Produces rapid and reliable reduction in myocardial iron Licensed second line if DFO not tolerated or ineffective Short half life (TDS or QDS dosing)	Reduction in heavily loaded patients may take years of regular therapy Lisenced as first line therapy
Contra-indications	Hyper-sensitivity	Previous agranulocytosis Pregnancy– teratogenic risk	Hyper-sensitivity eGFR <60ml/min Pregnancy
Cautions	Adherence Bone growth abnormalities Yersinia infection risk High-tone sensineural hearing loss	Arthropathy and GI disturbance reported Neutropenia risk (6.7% incidence in pooled trial data)	Self limiting rash reported in 10% Mild dose dependent increase in serum creatinine common Upper GI ulcers reported, avoid NSAIDs if possible
Monitoring	Monthly LFT Annual pure tone audiometry Annual ophthalmology	Weekly FBC Monthly LFT Audiometry and ophthalmology only if in combination with DFO	U&E: weekly during first month of initiation and dose change. Then monthly LFT: 2 weekly for first month. Then monthly Annual pure tone audiometry Annual ophthalmology

Required treatment depends on several factors, including the underlying diagnosis, patients

age, ROIL and current body iron load. Standard chelation is generally required for average ROIL, which in TDT is 0.3-0.5mg/kg of iron per day.

Monotherapy or combination regimes can be used, either simultaneously, sequentially or alternating. Selection should be determined by the site and severity

of iron overload, together with history of compliance, prior toxicity and patient choice.

Combinations are not recommended as first line but can result in enhanced efficiency of excretion of chelator-iron complexes.

- *Combined DFO and DFP*: most widely studied and used combination. Good evidence for reversing cardiac failure as a sequential or simultaneous regime. Adverse effects are common and precautions concerning monotherapy should be more closely monitored.
- *Combined DFO and DFX*: Limited data on clinical use, but seen as effective.
- *Combined DFX and DFP:* Potentially a highly effective combination and clinical experience is increasing. This may be recommended by tertiary centre and is now routinely commissioned by the NHS.

The chelation regime should be reviewed every 3 months and necessary modifications actioned. Modification of iron chelation should be in line with the BSH guideline, 2021.

Evidence of iron loading	**Action**
Acceptable iron stores: Ferritin 500-1500µg/L, LIC 3-7mg/kg dw and myocardial T2* >20ms	No indication for switch. If maintained acceptable stores on DFO monotherapy, can consider switch to DFX if adherence issues or at patients request.
Increasing or high iron stores **but no cardiac iron:** Ferritin >1500µg/L, LIC >7mg/kg dw and myocardial T2* >20ms	Review compliance/medication issues Possible Indication for switch. Consider options and refer to MDT
Moderately increased cardiac iron and satisfactory body iron stores: Ferritin 500-1500µg/L, LIC <7mg/kg dw and mycordial T2* 10-20ms	Indication for switch Consider options and refer to MDT
Moderately increased cardiac iron and high body iron stores: Ferritin >1500µg/L, LIC >7mg/kg dw and myocardial T2* 10-20ms	Indication for switch Consider options and refer to MDT
Severe myocardial iron: Myocardial T2* <10ms not clinically in heart failure OR Myocardial T2* <10ms clinically in heart failure	Indication for switch. Consider continuous DFO in addition to DFP Admit for long line and start continuous IV DFO induction. Combine with DFP as soon as possible.

Chelator toxicity is more likely when body iron stores are low or serum ferritin is decreasing rapidly.

If on desferrioxamine, calculate therapeutic index at each visit.

Aim to keep <0.025 to avoid over chelation.

1. Calculate mean daily dose in mg/kg: (daily dose in mg/kg divided by number of days used) x 7
2. Divide by serum ferritin = therapeutic index

Chelation in special circumstances

1. Pregnancy:
   - Women who are planning to get pregnant should undergo a period of intensive chelation to optimise levels prior to becoming pregnant
   - All chelator drugs should be discontinued as soon as pregnancy is diagnosed in cases of spontaneous pregnancy
   - DFX and DFP should be stopped 3 months before planned conception. DFO can be continued until the time of ovulation.
   - DFO may need to be re-introduced in the later stages of pregnancy but this will be decided on an individual case basis
2. Renal impairment
   - Can be difficult with little published data to guide recommendations
   - DFO is most likely to be used as there is the most data and experience
   - Individual case based decisions will be taken and discussed at HCC MDT.

Complications of TDT - Chronic

- *Metabolic bone disease*
  - Osteoporosis/ osteomalacia are common. Regular check of calcium and Vitamin D levels are necessary and replacement often required. Prescribe replacement dose if levels deficient and continue maintenance.
  - If hypogonadal, refer to endocrinology to consider HRT
  - General advice on lifestyle should be given (avoidance of smoking and excess alcohol)
  - Dexa scans are generally every 2-5 years as advised by metabolic bone clinic
  - Bisphosphonate therapy should only be given after consultation with bone clinic and discussion with multi-disciplinary team (MDT). This should be reviewed regularly.
- *Liver disease*

- Chronic liver disease can occur due to iron overload or viral infection (hepatitis C, B), gallstones, chronic liver disease and hepatocellular carcinoma. Hepatitis A and B vaccination is offered to all TDT patients. Response to Hepatitis B should be monitored.
- Ferriscan should be done at least yearly (aiming to keep at lower end of 3 to 7mg/g dry weight) and chelation intensified (see below) if significant iron loading. Deranged liver function occurs when LIC is >15mg/g.
- There should be an annual review of hepatitis serology (B and C) and referral to hepatology should be instigated if any evidence of active or chronic viral hepatitis.
- Patients who are Hep C RNA positive are at high risk of liver tumours and may therefore require lower liver iron targets (LIC <5mg/kg/dw). Eradication therapy can be given, but close monitoring of liver and cardiac iron is required and chelation adjusted accordingly.
- Patients with established cirrhosis should remain under hepatology follow up and require HCC monitoring with AFP/USS screening

- *Cardiac disease*
  - Symptoms of cardiac disease should be sought at each annual review (particularly dyspnoea, chest pain, palpitation) as well as regular cardiac T2* examination, ECG and echocardiogram.
  - If evidence of cardiac iron overload is found, chelation therapy should be maximised accordingly. This usually requirements the initiation of intravenous desferrioxamine.
  - All cases should be discussed in the Thalassaemia HCC MDT
  - Use of diuretic, ACE inhibitors and increased transfusion threshold should generally be made in conjunction with the local cardiology service.
  - Patients with long term indwelling lines or AF should be considered for anticoagulation
  - Cardiac monitoring should be performed in line with above recommendations.

- *Endocrine disease*
  - Regular monitoring via annual review to screen for diabetes, hypothyroidism and hypoparathyroidism. Any abnormality should be managed in conjunction with endocrinology department.
  - At least annual enquiry should be made about menstrual cycle and reproduction in female patients and sexual function and reproduction in males. Additional advice from the regional Thalassaemia MDT may be necessary in cases of severe iron loading and primary or secondary

amenorrhoea where pregnancy is desired.

- *Others*
  - *Splenic complications:* Splenomegaly results from the expansion of the reticuloendothelial system due to red cell destruction. The main indication for splenectomy would be to reduce transfusion requirements for those patients with an enlarged spleen. However patients with TDT who undergo splenectomy have a higher incidence of venous thrombosis, pulmonary hypertension along with the risk of post splenectomy sepsis. All cases should be discussed at the regional MDT prior to referral to consider splenectomy.
  - *Pancreatic Exocrine insufficiency:* Symptoms include abdominal cramps, weight loss, fatty stools and malnutrition. Request faecal elastase if clinical suspicion and refer to gastroenterology for specialist input.
  - *Dental Complications:* These may relate to previous bony expansion and/or be treatment related. Patients should be referred to Oral and Maxillofacial surgery (OMFS) for specialist review if concerns and appropriate dental review is advised prior to starting bisphosphonate therapy. Agreed pathway for dental referrals is as follows:
    - Any general dental issues - liaise with community dentist
    - Any emergencies - liaise with OMFS on call team
    - Any non-emergencies - send a referral to OMFS consultant

Complications of TDT – Acute

1. *Fever, infection and overwhelming sepsis*
   - Episodes of fever should be investigated with blood cultures, throat swab, mid-stream specimen of urine (MSSU) and swabs as appropriate. Manage in line with sepsis six protocol.
   - Atypical pathogens must be sought in those with previous splenectomy
   - White cell count should be checked in those on deferiprone because of risk of agranulocytosis
   - Desferrioxamine should be discontinued if symptoms suggestive of Yersinia (sore throat, high fever, abdominal pain, diarrhoea) and treatment commenced following discussion with local microbiology team
   - Antibiotics should be given according to local protocol
   - Additional transfusion may be required
   - Advice should be sought from Microbiology if persistent evidence of infection
   - *2. Hepatobiliary Complications* Those presenting with hepatic failure or significant hepatic impairment should be assessed by specialist liver team

- Investigations should include hepatitis viruses (hepatitis A, B,C, Epstein Barr virus (EBV), cytomegalovirus (CMV) as well as ferritin and assessment of overall iron loading), ultrasound for gallstones and lesions in liver
- Treatment for hepatitis C should be initiated by the specialist team
- Those presenting with jaundice above normal baseline should be assessed for gallstone obstruction or delayed haemolytic transfusion (if relevant)

2. *Cardiac decompensation*
    - Arrhythmia, worsening exercise tolerance, dyspnea and decompensated cardiac failure may occur
    - Immediate treatment advice should be sought from cardiology but will include beta blocker +/- Angiotensin converting enzyme (ACE) inhibitors +/- inotropes. Over diuresis with diuretics can precipitate acute renal impairment and should therefore be used with caution.
    - Iron burden and chelation therapy should be urgently reassessed and chelation intensified (consideration should be given to continuous intravenous desferrioxamine at high dose and combined use of deferiprone)
    - Transfusion therapy needs to be reviewed and extra transfusion may be required to keep post transfusion level around 120g/l (diuretic therapy may be required)
    - Ensure electrolytes are closely monitored and kept within optimal range.
    - Local cardiology involvement should be requested urgently and further advice sought from cardiology colleagues at a large tertiary centre. Arrythmia can be challenging and difficult to control and may require specialist review.

3. *Endocrine decompensation*
    - Rarely present urgently but may if not picked up on routine screening
    - Examples are : diabetic hypo- or hyperglycaemia, hypothyroidism or hypoparathyroidism (perioral or peripheral tingling, numbness or tetany)
    - Management is of underlying condition in collaboration with local medical teams
    - Iron status should be assessed in light of new symptoms
4. Thrombotic complications
    - These are well described in TDT and NTDT patients. Arterial events are less common but may present as patients age and have other cardiovascular risk factors

Considerations for patients with central venous catheter/CVC (taken from Thalassaemia HCC guideline):

- Thromboprophylaxis should be considered for all adult patients with thalassaemia 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, noting contraindications or unacceptable bleeding risks.
- In the context of CVC-associated VTE, CVC lines should only be removed if they are infected, non-functional or if there are progressive symptoms despite anticoagulation.
- If a CVC is removed, the patient should complete a minimum of 3 months of anticoagulation, then consider ongoing therapy based on their relative thrombotic and bleeding risk factors
- If the line remains in situ, the patient should continue anticoagulation for this period.
- Repeat imaging may be considered after 6–12 weeks, to ensure no thrombus progression.
- Advancing age, splenectomy, iron overload and long-term anaemia of <90 g/dL in patients with TDT and NTDT are known risk factors for VTE. Optimising both thalassemia and non-thalassemia risk factors is important to prevent and manage VTE.
- Patients identified to be at highest risk on their TRT-RSS should have their thalassemia care optimised to further reduce the risk of thrombosis.

Special circumstances

Pregnancy

Female patients who wish to plan a pregnancy should be referred to the obstetric haematology clinic for pre-pregnancy counselling. Assessment of risk to themselves and their offspring should be discussed, including partner screening.

- All pregnant women should be reviewed at local MDT and escalated to regional Thalassaemia MDT as required.
- A woman should be fully pre-assessed for her fitness for pregnancy pre-conception. This should incude:
    - A cardiology review, including yup to date T2* cardiac MRI and baseline echocardiogram
    - Assessment for diabetes by a glucose tolerance test (if non-diabetic) and fructosamine (if diabetic)
    - Assessment of thyroid function
    - Bone densitometry testing
    - Full medication review [oral iron chelation should be stopped 12 weeks prior to any planned fertility treatment; desferrioxamine can be continued until pregnancy test is positive].

Surgery

Surgical procedures should be planned as much as possible. To minimise perioperative

complications endocrine disorders should be well controlled; if possible optimise cardiac and liver iron if time permits. For patients with cardiac iron overload the stress surgery can precipitate heart failure.

- All patients should have an optimal haemoglobin pre-operative and there must be a clear management plan taking into account transfusion, anticoagulation, and management of endocrine disorders.
- Patients with TDT and NTDT are at increased risk of thrombosis, therefore perioperative thromboprophylaxis should generally be given to cover major procedures.

Non Transfusion Dependent Thalassaemia (NTDT)

Non transfusion dependent thalassaemia (or thalassaemia intermedia) is a clinical condition characterised by a higher haemoglobin than expected in those expected to be transfusion dependent (e.g. homozygous for β thalassaemia) or lower than expected (e.g. in certain individuals with heterozygous B thalassaemia). In either case the patient does not need regular transfusion but may do under certain conditions e.g. pregnancy.

Other causes include Haemoglobin H disease (severe alpha thalassaemia with 1 functioning alpha gene of 4) and less usual haemoglobin abnormalities e.g. Haemoglobin E β thalassaemia.

Diagnosis

Most individuals with NTDT will have been diagnosed during childhood. However new patients may present to the adult services, either on moving to the UK or with clinically less severe phenotype presenting for the first time in adulthood. Young adults moving through the transition clinic to the adult service should have a seamless review process and management plan documented in the notes and patient summary.

All patients will be registered on the NHR.

Assessment

Full history including reference to the following disease specific areas:

- Family origin
- Family History
- Growth and development, endocrine problems
- Transfusion History
- Medication
- Significant clinical events
- Psychosocial history

Examination with particular reference to any bony or orthodontic abnormalities, cardiac status, any hepatosplenomegaly, or evidence of endocrine dysfunction

Laboratory tests at diagnosis (or if not previously performed) should include:

- Full blood count, blood film and reticulocyte count
- Hb analysis by HPLC
- G6PD screen
- 5-10ml EDTA samples to, special haematology lab for red cell genetics via Cambridge GLH. Clinical details must also include red cell parameters, any relevant family history and family origin.
- Biochemistry screen including U&Es, LFTs, Calcium, Vitamin D level,

Lactate Dehydrogenase (LDH)

- Haematinics: B12/folate/ferritin, transferrin saturation
- Endocrine: Thyroid stimulating hormone (TSH), Blood glucose, sex hormone analysis
- Serum ferritin may underestimate liver iron, Ferriscan or equivalent should be done
- Echocardiogram
- Cardiac MRI T2* may be required if high ferritin or previous transfusion
- Extended red cell phenotype
- Virology screening

Suspected extramedullary haematopoiesis should be investigated promptly. If confirmed, radiotherapy can be considered if there is urgent need to alleviate pressure effects. Hypertransfusion and/or hydroxycarbamide may be appropriate alternative treatment options.

Management

1. Routine monitoring and folic acid supplementation
    - This should be offered to all NTDT patients

Monitoring requirements for non-transfusion dependent (NTDT) patients Frequency dependent on clinical severity: If moderate/severe phenotype, may be performed more frequently.	
Clinical assessment: To include - Height, weight, Spleen and liver size	At least annually
Blood tests: To include -	
FBC, LFTs, U&Es, Ferritin	At least annually
Investigations: To include – Echocardiogram Liver Iron quantitation by Ferriscan T2* Cardiac MRI DEXA bone densitometry	 Every 1-3 years At least 5 yearly, 1-2 yearly if moderate severity 2-5 yearly or more frequently if abnormal 2-5 yearly dependent on previous results 5 yearly, unless otherwise recommended

2. Transfusion
    - Patients may require intermittent transfusions during times of intercurrent illness or pregnancy. Increasing age increases the risk of

alloimmunisation.

- If required, ABO Rh and Kell matched blood should be transfused
- The decision to start regular transfusions depends on clinical and laboratory assessment, to include:
    - Worsening anaemia
    - Inability to tolerate anaemia
    - Massive splenomegaly
    - Worsening bone disease
    - Increasing nucleated red blood cells
    - Skeletal malformation can be severe in thalassaemia intermedia and should be considered in the decision to start transfusion.
- If transfusions are initiated this may not be a lifelong commitment and such decisions should be discussed at the regional MDT or in conjunction with tertiary centre

3. Splenectomy
    - Should be considered where there is significant splenomegaly causing clinical symptoms or hypersplenism.
    - Splenectomy does not provide a permanent alternative to regular transfusion so should not be advised in this regard.
    - However the risks of splenectomy (sepsis, thrombosis, pulmonary hypertension and enhanced iron loading) need to be balanced against possible benefit.
    - Review USS abdomen to exclude gall stones, which may be removed at the same time

4. Iron Chelation
    - Monitor as per TDT with LIC and T2* monitoring.
    - Deferasirox (7-21mg/kg) first line chelation unless contraindications.
5. Hydroxycarbamide
    - In some cases treatment with hydroxycarbamide may raise the Hb level sufficiently to avoid regular transfusion. The decision to use is based on the underlying condition, symptoms, patient preference and level of haemoglobin. If commenced, patients should start at a dose of 10-15mg/kg and the full blood count monitored regularly.
6. Bone marrow transplant
    - May be considered for some patients who have significant symptoms and are not able to receive transfusion therapy or hydroxycarbamide

7. Education and Training

Ongoing training for haematology trainees who will be involved in reviewing patients in outpatient clinic, as part of regional training Programme

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
NHS England haemoglobinopathy dashboard requirements	As part of quality dashboard	Amy Webster	Annually	SSQD

5. Supporting References (maximum of 3)

Standards for the clinical care of children and adults with thalassaemia in the UK, 3rd edition 2016

6. Key Words

Thalassaemia, chelation, iron overload monitoring

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr Amy Webster, Consultant Haematologist	**Executive Lead**
Details of Changes made during review: Updated to incorporate thalassaemia HCC guidance on thrombosis and Hepatocellular carcinoma monitoring AR paperwork appendix updated	

Appendix1: Thalassaemia Annual review paperwork

Patient Details (or affix addressograph) Name: Hospital number: DOB:	Name of reviewer: Date of review: Place of review: UHL / NGH / KGH / NUH / RDH / Other
	Diagnosis: NHR registered? Yes / No Card Issued? Transition patient? Yes / No Centre change in previous 12 months? Yes / No
Past Medical History	
General Health Update: **Consider physical, psychological, financial and emotional implications**	
General health review: Any new or ongoing concerns?	
Systems review: Review the following **Cardiovascular** **Growth, development and endocrine function** (Diabetes, endocrine replacement, sexual function) **Bone disease** **Liver** **Chronic Pain**	Please outline any specific concerns:
Has the patient undergone any surgery in the previous 12 months?	Yes / No If yes: Details:
In the past 12 months has the patient conceived a child?	Yes / No If yes: Details

Discuss fertility/contraception/pre-pregnancy counselling		
Transfusion and Chelation Review:		
Transfusion Regime Does the patient have any red cell antibodies?	**If not applicable, tick here** □ Yes / No If yes, details:	
Has the patient had regular transfusions during this period? If yes, what is the current regime?	Yes / No Frequency: Number of Units: Mean pre-transfusion Hb: Comments re: transfusion	
If no, has the patient had ad hoc transfusions during this period? Yearly blood volume transfused (mls/kg) Rate of Iron Loading (ROIL) (mg/kg)	Yes / No If yes, details:	
Chelation review If applicable, what is the current regime: Combined desferrioxamine + deferiprone Combined deferasirox + deferiprone Deferasirox Deferiprone Desferrioxamine Other	**If not applicable, tick here** □ Please outline dose and supply details: □ □ □ □ □	
Any complications/side effects?	Yes / No If yes, give details:	
Compliance issues?	Yes / No If yes, give details:	
Medication and Vaccination review: ***Relevant if previous splenectomy***		
Vaccination review: Influenza Pneumovax (PPV 23)	Tick all that apply: □ □	Date given:

Hep B Meningitis B Men ACWY Menitorix (Meningitis C + HiB) Prevenar (PCV13) Other (please specify)	□ □ □ □ □ □	
Medication review Bisphosphonate Folic acid Hormone replacement therapy Hydroxycarbamide Penicillin V Thyroxine Vitamin D Other (please specify)	Please outline dose and supply details: □ □ □ □ □ □ □ □	
Bone Marrow Transplant patient?	Yes / No If yes, details:	

Observations and Examination findings:

BP		Cardiovascular: Respiratory: Spleen size: Liver size: Other (please specify)
Oxygen Sats		
HR		
Weight		
Height		

Psychosocial review:

Psychosocial input: (highlight input required if applicable)	Referred to Psychology (not seen)	Psychology review ongoing or completed	Other Mental health input

Notes:

Routine Investigations:

Mandatory bloods: All patients			***Mandatory bloods: Transfusion Dependent Patients***			***Additional bloods: Maybe required in some patients***		
Test	*Date*	*Result*	*Test*	*Date*	*Result*	*Test*	*Date*	*Result*
Bone Profile			FSH/LH			PTH (if low calcium)		

Ferritin			Oestrogen (female)			***Additional investigations: required in patients as indicated***		
LFTs			Testosterone (male)			*Test*	*Date*	*Result*
U&E			TFT			Bone Densitometry		
Vitamin D			Viral Serology			Echo		

Specialist Investigations:

All patients on iron chelation			***Iron assessment***			
Test	*Date*	*Result*	*Test*	*Indicated:*	*Date*	*Result*
Urine PCR			Ferriscan	Yes No		
Ophthalmology						
GTT			Cardiac T2*	Yes No		
Audiology						

Management Plan

Investigations required?	Yes / No Details:
Specialist referral indicated?	Yes / No Details:
Other actions discussed:	Yes / No Details: Transfusion plan (where applicable): Chelation plan (where applicable):

Interested in research studies?	Yes / No
MDT referral required? *(Note if NHP referral required or completed)*	Yes / No
Follow up appointment	

Appendix 2 – List of contact clinicians - Leicester

Renal:	Dr Reem AlJayyousi, Consultant Nephrologist Dr Jorge Jesus-Silva Consultant Nephrologist	LGH 0116 258 4195 LGH 0116 258 4132
Bone disease:	Dr Faizanur Rahman, Consultant Chemical Pathologist	LRI 0116 258 6560
Orthopaedics:	Hip: Mr Andrew Brown/Mr Steffan Hutchings	LGH 0116 258 4217
Ophthalmology:	Mr James Deane, Consultant Ophthalmologist	LRI 0116 258 6864
Cardiac:	Dr Ian Loke, Consultant Cardiologist	GGH 0116 258 3036
Cardiac MRI:	Dr Aparna Deshpande, Consultant Radiologist	GGH
Respiratory: (including sleep disorders)	Dr Alys Scadding, Consultant in Respiratory Medicine	GGH Leicester 0116 250 2640
Endocrinology:	Dr Miles Levy, Consultant Physician and Endocrinologist Dr Ragini Bhake, Consultant Physician and Endocrinologist	LRI 0116 258 5866 0116 258 5157
Dental/Maxillo-facial	See guideline for agreed pathway	Oral & Maxillofacial Surgery 0116 258 5301

Appendix 3 – Quick reference guide

Transfusion Dependent Thalassaemia: UHL guideline pages 2-8		
Transfusion	Aim pre transfusion Hb 90 to 105 g/l Use fresh Rh phenotype and Kell appropriate red cells Prompt time to needle (<30 minutes) with minimal venepuncture attempts (<3) Follow local transfusion policies	Outreach for pre transfusion bloods Out of hours transfusion should be possible Occasional post transfusion FBC
Annual review	Undertaken at specialist centre – see text for details and list of investigations	Referral to HCC MDT
Iron monitoring	Ferritin 3 monthly Cardiac T2* MRI 1-2 yearly Ferriscan or equivalent for liver iron overload 6-12 monthly	Cardiac T2* >20msec - no cardiac iron overload Target liver iron 3- 7mg/g dry weight
Chelation	Individual plan in association with the patient and specialised service: 3 drugs available desferrioxamine, deferiprone and deferasirox	Monotherapy or combination therapy based on ROIL, age, co-morbidities and current iron status
Chronic complications: UHL guideline pages 8-10		
Cardio-vascular	Cardiac failure Arrhythmia	Refer cardiology Reassessment of cardiac iron status Screen for arrhythmia – high risk if previous cardiac iron
Impaired glucose tolerance	Regular testing of OGTT	Good medical management by specialist diabetic service Intensify iron chelation
Bone problems	Osteopenia/ osteoporosis	Regular DEXA scan Optimise vitamin D HRT should be considered Bisphosphonates could be used , generally with input from metabolic

		team
Liver problems	Chronic hepatitis/Cirrhosis Obstructive jaundice Portal hypertension Hepatic insufficiency Hepatocellular carcinoma	Monitor LFTs every 3 months Optimise liver iron Check viral serology yearly Refer specialised liver unit if viral hepatitis, cirrhosis
Dental	Awareness of likelihood of problems in those where transfusion therapy inadequate in childhood Osteonecrosis can occur with bisphosphonates	Collaborative approach Infection may be a particular risk
Acute complications: UHL guideline pages 10-12		
Cardiac: arrhythmia, cardiac failure	Urgent assessment (ECG& Echo) Senior cardiology review Likely to require IV desferrioxamine and deferiprone for high cardiac iron load	Fu cardiac MRI T2* with appropriate change to chelation
Sepsis	Sepsis 6 interventions Yersinia can occur May be non-specific especially in iron overloaded patients	Look for other issues e.g. gallstones, attention to post splenectomy, antibiotics. Gallstones and renal stones more common
Endocrine	Acute complications of diabetes, calcium metabolism	Regular endocrine monitoring will identify
Liver	Cirrhosis Variceal bleeds	Monitoring liver function Early referral to Hepatology
Special Circumstances: UHL Guideline pages 12-13		
Pregnancy	Ensure optimal fertility with use of iron chelation o Pre-conceptual counselling and through assessment Risk of cardiac problems, worsening iron chelation , infection, thrombosis, higher operative delivery risk Consider baby risks	Combined care – refer all cases to HCC MDT for discussion Desferrioxamine can be used in 2nd and 3rd trimester and should be used at delivery

Non-Transfusion Dependent Thalassaemia: UHL Guideline 14-16		
Comprehensive assessment	DNA Growth & development	Regular monitoring required
Transfusion	Need for intermittent or long term	Red Cell Phenotype match mandatory. Regular review of transfusion requirement
Splenectomy	Consider if hypersplenism or massive splenomegaly	Usual splenectomy – discuss at HCC MDT before referral
Iron overload	Ferritin is unreliable. Iron accumulation can occur even if not transfused	Usual iron monitoring including MRI, T2* & Ferriscan (although heart iron accumulation is less frequent)
Pulmonary Hypertension	Occurs in up to 30% un-transfused adults	Regular echocardiography with referral to regional service if suspected.
Extra medullary haematopoiesis	Asymptomatic paravertebral masses occur in 15 – 20%	May require treatment depending on anatomical position
Liver	Transfusion transmitted infection	Yearly screening for hepatitis B and C
Low bone mineral density (BMD)	Very common	May require regular transfusion therapy
Treatment Options	Hydroxycarbamide: Variable response Stem cell transplant: Careful consideration of pro's & cons	Requires review at HCC MDT