Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK

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Writing Group

The following individuals contributed directly to the writing process.

- Dr Anne Yardumian, Consultant Haematologist, North Middlesex University Hospital, London (Chair of Writing Group)
- Dr Paul Telfer, Senior Lecturer in Haematology, St Bartholomew's and The Royal London Hospitals NHS Trust, Queen Mary, University of London
- Mr George Constantinou, patient representative, UK Thalassaemia Society
- Dr Phil Darbyshire, Consultant Paediatric Haematologist, Birmingham Children's Hospital
- Mr Matthew Darlison, Senior Research Fellow Clinical & Applied Bioinformatics, University College London Centre for Health Informatics and Multiprofessional Education (CHIME)
- Dr Sally E Kinsey, Consultant Paediatric Haematologist, St James' University Hospital, Leeds
- Mrs Elaine Miller, Co-ordinator, UK Thalassaemia Society
- Professor Bernadette Modell, Emeritus Professor of Community Genetics, University College Hospital London and UCL Centre for Informatics and Multiprofessional Education (CHIME)
- Dr Melanie Pollitzer, Associate Specialist, Paediatrics, Royal Berkshire Hospital, Reading
- Professor John B Porter, Professor of Haematology University College Hospital London
- Emma Prescott, Thalassaemia Nurse Specialist, Whittington Hospital, London
- Mrs Katerina Read, patient representative, UK Thalassaemia Society
- Dr Christos Sotirelis, patient representative, UK Thalassaemia Society
- Dr Rachel Spector, Clinical Psychologist, Birmingham & Solihull Mental Health Trust
- Dr Christine Wright, Consultant Haematologist, Sickle Cell & Thalassaemia Centre, City Hospital, Birmingham

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The UK Thalassaemia Society can be contacted at:

19 The Broadway,
Southgate Circus,
London,
N14 6PH

Telephone

020 8882 0011

Fax

020 8882 8618

E-mail

office@ukts.org

Website

http://www.ukts.org/

Foreword to the 2nd Edition

from the UK Thalassaemia Society

When we introduced the first edition of *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK* in 2005, we were well aware of the need for a clear, concise document giving details of the optimum treatment for thalassaemia. We were therefore not surprised when our first print run of 1000 copies lasted only a few months. Since 2005 we have distributed 2000 hard copies to health professionals and patients, not only in the UK but worldwide; not to mention the many hundreds of copies which were given out on CD-ROM and downloaded from our website.

As a thalassaemic now well into my forties I am acutely aware that we who live with this condition have a responsibility to be active participants in our treatment rather than mere passive recipients. One of our goals in producing the first edition was to empower patients in seeking the highest standard of treatment. Since 2005 there have been notable advances in treatment, particularly in the field of chelation. Again, we hope that this book will be of use to both health professionals and patients in obtaining their own, individually tailored optimum treatment regimen. We are fortunate to have centres of excellence for thalassaemia in the UK; where the standard of treatment is as good as anywhere in the world. We will not rest until this high standard of care is available to every thalassaemic in the UK.

The UKTS thanks the original Writing Group, all the reviewers and in particular the principal authors Dr Anne Yardumian and Dr Paul Telfer for their many hours of dedicated work in revising and updating the book. Special thanks also go to Dr Phil Darbyshire and Mr Matthew Darlison for their valuable assistance

With best wishes,

Michael Michael
President, UK Thalassaemia Society

from the Department of Health

We welcome this update of the standards for the delivery of care to patients with Thalassemia and we strongly support it.

The document has benefited from the involvement of patients in the development and the process of implementation. Empowerment of patients and the public is an essential aim of the NHS and the Thalassemia Community should be proud of their effort.

Clinicians who have embraced these standards will have seen improvements in their services through the Peer Review Process, and commissioners will be pleased to see these improvements translated into better outcomes.

We are sure that this document will be also be an invaluable source of information to commissioners when developing future services for patients.

William Connon
Head of Blood Policy
Infectious Diseases & Blood Policy
Department of Health

Denise O'Shaughnessy
Consultant Haematologist
and Senior Medical Advisor
Department of Health

Contents

Summary

of Standards

Section A: Organisation of thalassaemia services

Standard: Networks for Care

- All regions in England should be covered by a clinical network incorporating local thalassaemia Clinics and one or more Specialised Thalassaemia Centres.
- Procedures within the network should ensure that all patients have access to a specialist Centre, either for their regular care if living nearby or for regular review at least once a year, and for additional specific consultations as needed, if living more distantly.
- The network should have sufficient resources (health care professionals, management and administrative staff) to function effectively, and should develop systems for information sharing, clinical governance, accountability and staff development.
- A 'Key Contact' health professional will be designated for each patient.
- Patients and carers should receive regular education, supervision and support in thalassaemia care, chelation therapy and other home treatments.
- Hospital admissions should be minimised by adequate monitoring, management of chelation, and early identification and treatment of complications.
- Local Clinics and apecialised Centres within the network, should record and exchange information relating to clinical events monitoring investigations, and changes in treatment. Information should be shared with patients, carers and GP's.
- Patients and carers should be involved in making decisions about management and delivery of care. They should be encouraged to follow progress by receiving copies of clinical letters and recording important information in a hand-held record.
- Patients and carers should have access to peer support groups.

Section B: Core Management Standards

Standard: Initial management of the newly diagnosed infant.

- Diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate. It should be established as soon as possible after birth, and should include genotype.
- The child must be monitored closely to determine the likely clinical course.
- The family should be informed fully and sensitively from the outset, by appropriately experienced professionals, with the use of a culturally-appropriate health advocate if necessary, and with the opportunity for full discussion. Suitable written information should be given to them.
- A management plan tailored to the individual child must be agreed and implemented.
- The family should be encouraged to give consent for the child's details to be recorded on the UK Haemoglobinopathy Registry.

Standard: Decision to Start Regular Transfusions

- Infants with β thalassaemia will be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion will be started promptly when there is sufficient clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity.
- Infants and children with a thalassaemia intermedia phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

Standard: Red cell transfusions

- Haemoglobin levels should be maintained above 9.5-10g/dl.
- Cannulation will be undertaken by an experienced nurse or doctor.
- Pre-arranged transfusions should be started promptly.
- Good transfusion practice must be observed
- Transfusions will be given on each occasion in a designated area with suitable facilities, experienced regular named nurses and familiar supervising medical team.

Standard: Iron Load - Monitoring and Treatment

- A protocol for iron chelation therapy in children and adults, based on current published evidence, expert opinion and local conditions should be used in the Thalassaemia Specialist Centre and local centres of the clinical network and reviewed at regular intervals.
- Chelation modalities shown to be clinically beneficial (desferrioxamine infusions, deferiprone, deferasirox, combination therapy with desferrioxamine and deferiprone) should be prescribable and recommended according to indications stated in the protocol.
- Decisions about initiating and changing chelation therapy should be made by the thalassaemia specialist, taking into account the informed preferences of the patient and carers, and other health care workers involved with the patient. Time should be taken to explain the benefits and possible adverse effects of each option, using written information in the appropriate language, and health advocacy if required. The decision process should be recorded in the patient's records.
- Patients and carers should be supported in adhering to chelation therapy using a multidisciplinary team approach which includes clinic doctors, nurse specialists, clinical psychologists, play therapists etc. Adherence should be monitored regularly, and problems carefully identified and addressed. Patients should be encouraged to use a treatment diary (e.g. UKTS hand-held record) to assist with monitoring.
- All patients should have access to MRI modalities (Cardiac T2* MRI and either R2 or T2* of liver) for monitoring myocardial and liver iron.
- Patients should be carefully monitored for side effects of iron chelation therapy according to the local chelation protocol, and treatment interrupted or reduced promptly to avoid serious toxicity.
- The outcomes of chelation therapy within local clinics and the network (including measures of iron status, clinical evidence of iron-related tissue damage, adverse effects of chelators and quality of life) should be audited regularly using the local protocol as an audit standard. Results of audits should be anonymised, and discussed with the thalassaemia care teams within the network and local patient interest groups and acted upon promptly.

Standard: Psycho-social Issues

- The psycho-social needs of patients growing up with thalassaemia must be considered alongside every aspect of their clinical care. This is a key role for all professionals managing the child, to be considered in each communication with the child and family.
- Core staffing of specialist thalassaemia Centres should include a Clinical Psychologist.

Standard: Acute Clinical Presentation in the Treated Patient.

- Individual presenting to their primary care professionals, or a hospital A&E Department or clinic, with new symptoms and/or signs will be rapidly assessed by staff aware of the various acute complications which can occur in this condition.
- If staff with appropriate knowledge and experience are not available, there must be urgent consultation with members of the specialist team on site or at the Centre, and referral on after stabilisation, as necessary.
- Appropriate management should be instituted as quickly as possible.
- GPs of patients with thalassaemia should be aware of the range of acute complications thay can encounter.

Standard: Referral for Consideration of Bone Marrow Transplantation

- All families who have a child with a serious thalassaemia syndrome will be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, usually around 12 - 18 months of age.
- Referral does not depend upon the family having an available donor at the time, and discussions may inform the family's subsequent decisions on family size.
- The discussion must be with a transplant team with specific experience in transplanting for thalassaemia.

Standard: Surgery including Splenectomy

- Surgical procedures requiring general anaesthetic should be undertaken at, or after consultation with, the thalassaemia specialist Centre.
- Patients should be carefully assessed pre-operatively with special reference to cardiac, endocrine and metabolic disturbances which may require correction.

Standard: Transition from Paediatric Care and Management of Adults

- Transfer from paediatric to adult care must be planned in advance for each individual, and timed to take into account his or her level of physical and psychological development.
- The young person will be familiar with the staff and facilities of the adult services prior to transfer.
- As far as possible management protocols and care pathways, including how to access acute care, should continue seamlessly from paediatric to adult services, but where this is not the case any differences should be highlighted and explained to the young person to avoid confusion.
- In young adults, active vigilance is required for development of clinical complications, so that appropriate management can be instituted.

Section C: Prevention and management of complications

Standard: Cardiac Complications

- A cardiologist should be identified for each clinical network, to collaborate with the haematologists in developing protocols, offering cardiac surveillance and care of patients with cardiac complications. Paediatric centres should identify a paediatric cardiologist to fulfil this role
- Patients should have a regular cardiological assessment from age 10.

- Myocardial iron should be monitored by Cardiac T2* from age 8 years. Cardiac T2* should be maintained >20 milliseconds by appropriate adjustment to chelation therapy (see chapter 7).
- Other common disorders seen in thalassaemics which can adversely affect cardiac function (e.g. hypothyroidism, hypocalcaemia, uncontrolled diabetes, acute infection, thrombosis, pulmonary hypertension) should be subject to regular monitoring and treated promptly
- Any symptoms or signs suggestive of cardiac disturbance should be taken seriously, investigations and management should be instituted urgently

Standard: Endocrine Complications

- A paediatric and an adult Endocrinologist will be designated for each specialist Centre.
- Children should be monitored regularly and systematically for growth and development, from diagnosis up until the time when they have achieved full sexual maturity and final adult height.
- Deviations from expected pattern should be investigated and managed promptly. Children who are found to be growth hormone deficient should receive replacement therapy.
- Patients from age 10 should be checked annually for biochemical evidence of glucose intolerance, and from age 12 for hypothyroidism and hypoparathyroidism, and deficiencies treated appropriately.

Standard: Liver Complications

- Liver function tests should be monitored regularly.
- Liver iron levels should be maintained within safe limits to avoid progressive hepatic damage.
- Adjustments to chelation or other treatment should be made if liver dysfunction is associated with therapy
- Transmission of viral hepatitis by transfusion should be minimised by avoidance of transfusion in some countries outside of the UK, where blood quality control is not so rigorous. Vaccination against hepatitis B infection should be standard practice.
- Liver disease should be managed in jointly with a designated Hepatologist.
- Chronic Hepatitis C virus infection should be managed actively, including histological staging and antiviral therapy aimed at sustained viral clearance.

Standard: Bone Complications.

- Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Bone changes related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.
- All patients should be encouraged to exercise, maintain a diet rich in calcium and vitamin D, avoid smoking and excessive alcohol consumption.
- Diagnosis of hypogonadism and other endocrinopathies should be prompt, and adequate hormone replacement therapy given.
- Teenage and adult patients will be monitored for osteoporosis.
- Established osteoporosis in adults should be treated with bisphosphonates.

Standard: Fertility, and Management of Pregnancy.

- Pubertal development, growth, and endocrine function will be closely monitored and prompt referral to the appropriate Endocrinologist made if there is any suspicion of problems.
- Women contemplating pregnancy will be assessed for possible risks to themselves and their babies and this evaluation up-dated as needed.
- At any time when the patient wishes she/he should be referred to a Gynaecology (fertility) clinic with experience of thalassaemia patients, to allow discussion about treatment options. Culturally appropriate advocacy in these discussions is imperative.

- Women should be jointly managed during pregnancy by a 'Maternal Medicine' Obstetrician experienced with thalassaemia, and by their Haematologist.

Section D: Specialist Review

Standard: Annual Review at Specialist Thalassaemia Centre.

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually at a thalassaemia Centre, with a team of health care professionals who have particular experience in the field.
- This should allow for broad discussion of treatment options, including any new information which has become available, and an individual treatment plan for the next 12 months will be confirmed.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre.

Standard: Review of Patients Previously Treated Outside the UK

- Children and adults who have been receiving treatment outside the UK will, on arrival, be seen promptly at an established Centre and thoroughly assessed.
- Any complications which may have developed will be detected and discussed with the individual and family and management plans made accordingly.

Section E: Management of thalassaemia intermedia

Standard:

- A comprehensive DNA diagnosis (β globin mutations, α globin genotype, Xmn1 polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established. Detailed consideration will be given to clinical and laboratory findings in order to reach a decision about transfusion and other treatment needs.
- Parents, carers, and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and therapeutic options available
- During the first 3-5 years of life, children suspected of having thalassaemia intermedia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy
- Children, adolescents and adults with this condition should continue to be monitored regularly, in conjunction with the specialist Centre
- Complications of thalassaemia intermedia should be minimised by anticipation, early detection, and appropriate treatment.

Introduction

1

Context, and the Aims of this Document

1.1 Thalassaemia in the UK

Modern treatment of thalassaemia is, for the most part, a success story. Children are surviving to adult life in good health, are able to lead essentially normal lives and have families of their own (Weatherall and Clegg 2001). Unfortunately, this outcome has not been universal in the UK. Premature deaths still occur, and children still develop complications such as growth failure and hypogonadism due to endocrine damage. These complications are related to transfusion iron overload, and the ability to adhere to iron chelation therapy (Modell and Berdoukas 1984, Olivieri et al 1994, Brittenham et al 1994). Outcomes are better in some specialist centres than in the UK as a whole (Modell et al 2000, Porter and Davis 2002). This suggests that some aspects of care can be unsatisfactory in smaller, less specialised clinics.

The majority of thalassaemic patients in the UK have been managed in clinics of less than 10 patients (Modell et al 2001) reflecting the patchy geographic distribution of patients. Difficulty in accessing optimal, patient-centred services can be a factor in reduced patient adherence to recommended treatment, leading in some cases to early death. Some progress towards reconfiguring services to redress this, by developing networks of care, has been made since the 1st edition of this document was published in 2005 but further work is needed to ensure that our original aim - that every patient should have access to optimal, specialist management guidance, as well as routine care provided conveniently close to home - is being realised for everyone.

1.2 Improving thalassaemia care

In the early 2000's, the UK Thalassaemia Society recognised the problem and demanded action. The Government's NHS plan published in July 2000 envisaged investments and reforms to transform the NHS into a patient-centred service. The plan included a commitment to a linked antenatal and neonatal screening programme for haemoglobin disorders, now realised as the NHS sickle cell and thalassaemia screening programme[1], which can be expected to identify the majority of neonates affected with thalassaemia throughout the country.

At the same time, the documents 'The New NHS' and 'A First Class Service - quality in the New NHS' introduced a range of measures to drive up quality and decrease variations in services, including the programme of National Service Frameworks (NSFs). These set national standards, define service models for their target patient group, put in place strategies to support implementation and establish performance milestones against which progress can be measured. The NSFs and other related NHS initiatives have direct relevance to the care of children and adults with thalassaemia. The National Service Framework for Children impacts on the hospital care of young thalassaemics, and the NSF for people with long term conditions contains much that is relevant to organising services for people with thalassaemia. Issues of inequality in access to health care are important since people with thalassaemia originate from ethnic minority populations . In parallel, a broad re-evaluation of how best to manage long-term or chronic health problems has continued, with focus on patient choice and involvement in their services. The National Service Frameworks especially emphasise the importance of user involvement, and The Expert Patient Programme[2] aims to empower patients with chronic conditions to manage aspects of their condition which are traditionally poorly addressed within conventional services.

1. http://www.screening.nhs.uk/sicklecellandthalassaemia/index.htm
2. http://expertpatients.co.uk/public/default.aspx

Recommendations and themes from these initiatives continue to be reflected in this updated edition of our standards for thalassaemia care in the UK.

In the three years since the first edition, there has been some real progress towards the goals we outlined. The NHS Sickle Cell and Thalassaemia Screening Programme, part of the UK Newborn Screening Programme, has successfully rolled out neonatal screening across England, and systematic antenatal screening is almost there, testing all pregnant women in high prevalence areas, and according to a family origins questionnaire in low prevalence areas[1]. The Screening Programme explicitly supports the development of Clinical Networks, working towards early and equitable access to optimal care for affected newborn as well as children and adults already attending clinics. Through the UK Forum for Haemoglobin Disorders, a comprehensive set of Quality Requirements[2] drawn from the 1st Edition of these Standards, and the sister document 'Sickle Cell Disease in Childhood; standards and guidelines for clinical care' 2006[3] has been agreed. A system of Peer Review visits, to assess service provision across proposed networks for care against these Quality Requirements, is planned. There is work ongoing to establish which aspects of haemoglobinopathy clinical care should be regarded as specialist services and commissioned on a regional level, and to designate specialist treatment Centres. To help inform appropriate commissioning, a National Haemoglobinopathy Registry is being launched[4] to collect information systematically regarding numbers of affected people attending the various centres, and to record certain aspects of their clinical care and outcomes. It is expected that this will help negotiate for further service improvements and inform healthcare planning. In parallel there are discussions regarding how care can best be funded within the DH 'Payment by Results' process.

Professor Lord Darzi's report 'High Quality Care for all' (June 08)[5] with its stated intention of developing services which are fair, personalised, effective and safe, builds on the earlier national service frameworks for children and for long-term conditions, and further supports the process of service improvements for haemoglobin disorders.

1.3 Aims and scope of these Standards

In this document we have outlined a model of care, and have defined standards for delivery of care, for patients with thalassaemia. We have addressed predominantly the needs of those who are transfusion dependent (thalassaemia major), and, in a separate section those who are not transfusion dependent (thalassaemia intermedia, section E). It is not intended to offer full clinical guidelines as these are well covered in other available published guidance. Where a subject is not well covered in other publications, more details are included, for example presentation of the acutely ill patient (chapter 9) and the management of patients starting treatment in the UK who have previously been treated elsewhere (chapter 19). Overall our central focus is on the way in which services are structured and delivered.

However, over the last three years there have been significant advances in the specifics of care for people with thalassaemia, and evidence of continued improvement in life expectancy. In particular, the use of the oral iron chelator deferiprone, alone and in combination with desferrioxamine, has continued to grow and its efficacy in improving cardiac iron complications has been established. The additional licensing of deferasirox has further broadened chelation treatment options, and our understanding of the appropriate use of the various regimens now available continues to be refined with the publication of new studies. These important changes in care are reflected in major revisions, for this 2nd edition, in the chapters about iron load - monitoring and treatment (chapter 7) and cardiac complications (chapter13). Other chapters have been updated where there have been important publications in the interim; these revisions are mostly relatively minor.

1. http://phs.kcl.ac.uk/haemscreening/Documents/F_Origin_Questionnaire.pdf
2. http://sct.screening.nhs.uk/Documents/QualityRequirementsSCTV1.pdf
3. http://phs.kcl.ac.uk/haemscreening/Documents/DETAILED_CLIN_Oct19.pdf
4. http://www.nhr.nhs.uk/
5. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085825

A further change is the inclusion of Quality Requirements (Appendix C), as referred to above, replacing the first section of the previous 'Fair Access to and Effective Delivery of Healthcare' performance indicators. The 'Health Outcomes of Care' section remains and it is hoped that this will be used by treating clinics and centres as a complementary tool. These indicators are intended to form the basis for a UK-wide peer review programme of care networks, starting in the near future. They are expected to provide a framework for commissioning authorities, to help them to ensure that the services they are supporting provide appropriate quality care.

Appreciating the central role of patients in planning and implementing changes, we have as before included at the start of each section, a number of relevant quotations, derived largely from focus groups and questionnaires organised by the UK Thalassaemia Society. We hope that these enliven the text, as well as giving insight into problems as seen from the patients' perspective.

The document is aimed primarily at healthcare professionals who care for people with thalassaemia, and technical terms are mostly used without explanation in the text. However, it is likely that some of it may be of interest or value to patients and their families, and a Glossary is included (Appendix E) to try to facilitate understanding of what may be unfamiliar terms.

1.4 Levels of evidence

Wherever possible, we have established a base in published research for proposals made. As noted, there has been a minor explosion of publications on the newer iron chelators and various regimens for their use, and about cardiac siderosis, which we have tried to review systematically in chapters 7 and 13. In most other areas, as previously, we have relied largely on published retrospective analysis of clinical data and non-randomised, non-controlled interventions, expert opinion, and the views of patients and families.

We have adopted a simplified form of grading evidence, which essentially recognises three Grades: A, B and C (Petrie et al 1995, Appendix D). The 'Key Interventions' are all graded, but as the great majority are Grade C, only for those which are other than Grade C is this specifically indicated.

1.5 Conclusion

In summary, we feel that there is cause for real optimism in the way that services for the management of thalassaemia and sickle cell disease are developing in the UK. We trust that everyone working in thalassaemia clinics across the UK will read these standards and apply them locally. Additionally, we expect health service managers and commissioners to be fully aware of the challenges presented by managing these disorders and to ensure equitable, high quality care for all those affected. We hope that patients and user groups will also find the document helpful, supporting them in negotiating for the best possible care.

2

Thalassaemia: Clinical Features and Treatment

2.1 Pathophysiology and geographical distribution

Beta (β) thalassaemia is a genetic disorder of haemoglobin production. It is inherited in an autosomal recessive pattern (apart from in vary rare 'dominant thalassaemia' mutations), and is common in people originating from the Mediterranean, the Middle East, South Asia, South East Asia and the 'Far East'. In the UK, β thalassaemia major is more or less restricted to ethnic minority populations, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi (Modell et al 2001) The disorder is due to a range of mutations associated with the beta globin gene, resulting in reduced or absent production of β globin, one of the constituents of the adult haemoglobin molecule (HbA). Reduced β globin production, leading to excess free α globin chains, damages red cell precursors in the bone marrow. This results in ineffective erythropoiesis, severe anaemia and compensatory erythroid marrow hyperplasia.

2.2 Classification

The thalassaemias can be broadly categorised clinically as:

- β thalassaemia major (BTM) in which haemoglobin production is so reduced that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy. Death at an early age is inevitable if no transfusions are given. Where the term 'thalassaemia' is used without qualification, it usually refers to β thalassaemia major.
- β thalassaemia intermedia (BTI) in which a reduced amount of haemoglobin is produced, sufficient for growth and development without the absolute requirement for regular transfusions. Growth may fail, and other complications may develop, in later childhood and adulthood, requiring regular transfusions to start.

The compound heterozygous states of β thalassaemia with a thalassaemic haemoglobin variant (Including HbE, Lepore, Knossos) or an alternative thalassaemic mutation (e.g. δβ thalassaemia) often result in a thalassaemia intermedia phenotype, but can cause thalassaemia major.

- Haemoglobin H disease and Alpha (α) thalassaemia major arise as a result of deletion of three or four of the four globin genes or from non-deletional mutations which inactivate them. If all 4 α globin genes are affected, the result is typically intrauterine anaemia and usually the early stillbirth of a hydropic infant (Bart's Hydrops fetalis) as α globin chains are required to form fetal haemoglobin. The next most severe form of α thalassaemia, when 3 of 4 α genes are affected, is known as Haemoglobin H disease and is usually a mild condition with features typical of a chronic haemolytic anaemia, although a few individuals develop more severe problems, including transfusion dependency.

These standards apply to transfusion dependent patients and those with thalassaemia intermedia (section E).

In a small number of cases worldwide to date, it has proved feasible, if prenatal diagnosis establishes that a fetus has α thalassaemia major, to give intra-uterine transfusion to sustain it until birth. This treatment needs to be started early, as otherwise serious disability results. After birth, such an infant will need to continue on a regular transfusion regimen as for β thalassaemia major. Separate guidelines

are necessary for the antenatal management of this condition.

2.3 Haemoglobinopathy screening

Population and antenatal screening to identify carriers of β thalassaemia is technically easy and cheap. Identification of a carrier parent, usually the mother, followed by testing of the partner allows identification of couples at risk of having an affected child. Having been counselled they can make informed choices about prenatal diagnosis and termination of an affected fetus. The effective delivery of this service has led to a great reduction in affected births in Mediterranean countries (e.g. Cyprus, Italy, and Greece). Delivery had been inconsistent across the UK (Modell et al 1997), but systematic screening of pregnant women in England is now in place, through the NHS Sickle Cell and Thalassaemia Screening Programme for linked antenatal and newborn screening.

Newborn screening is primarily aimed at detecting babies with sickle cell disease, in whom early interventions can prevent fatal complications before clinical presentation. However, most babies with β thalassaemia major will be identified by the same screening test, and early diagnosis can reduce morbidity associated with late presentation, and anxiety for affected families.

2.4 Clinical features of untreated thalassaemia

Babies with homozygous β thalassaemia are initially asymptomatic, as the major haemoglobin at birth is fetal haemoglobin (HbF). As a result of the physiological switch from HbF to HbA, the latter becomes predominant by about four to six months of age, and it is from this stage onwards that infants with thalassaemia major can become symptomatic. Clinically, the presentation is insidious, with poor feeding, faltering growth, pallor, and increased susceptibility to infection. If untreated, progressive anaemia and metabolic stress eventually cause heart failure and death. There is enlargement of the liver and spleen. The ineffective expansion of the erythropoietic marrow results in bone thinning and deformity. Untreated, children with β thalassaemia major die from heart failure or infection before the age of five.

2.5 Standard treatment

Standard treatment consists of regular blood transfusions given every three to four weeks. Transfusions correct the anaemia, enable growth and normal activity levels, prevent enlargement of the spleen and inhibit the erythroid marrow expansion. The most important long-term problem associated with regular transfusions in thalassaemia is iron overload. Blood contains iron which cannot be excreted from the body, and a typical thalassaemia patient on a regular transfusion programme will accumulate 0.3-0.5mg/kg of iron per day. Excessive iron is toxic, the most vulnerable organs being the heart, liver and endocrine glands. Once the body has accumulated 12-24g of iron significant clinical manifestations of iron toxicity can be expected (Gabutti and Borgna-Pignatti 1994). Without treatment to remove the iron, the majority of patients developed cardiac problems and died of heart failure by the age of 20. Therapy to remove or 'chelate' excess iron is therefore essential and this must be started within a year of so of starting regular transfusions. The established regime requires subcutaneous infusions of the chelating agent desferrioxamine given 5-7 nights per week over 8-12 hours. This regime can stabilise the body iron load at an acceptable level in a majority of patients, and has been shown to reduce the risk of cardiac disease, and to improve survival (Modell and Berdoukas 1984, Olivieri et al 1994, Brittenham et al 1994). Other complications of iron overload, such as short stature and hypogonadotrophic hypogonadism may also be prevented (Olivieri 1997). Standard treatment for many now includes the possibility of using a licensed oral iron chelator, either deferiprone (Ferriprox*, Swedish Orphan) or deferasirox (Exjade*, Novartis) (chapter 7). These can help greatly where adherence to parenteral desferrioxamine infusions has been a problem.

2.6 Adherence to treatment

The main problem with iron chelation therapy has been adherence to the regular subcutaneous infusions of desferrioxamine. The infusions are time consuming to set up,

and require introduction of a subcutaneous needle on each occasion followed by continued attachment to an infuser device over 10-12 hours. They are unpopular and often resisted, especially by older children and teenagers, because they can cause local discomfort and because having to undertake this onerous self-treatment sets the child apart from his or her peers. In a large, well organised thalassaemia Centre, physical and psychological problems with adherence can be addressed methodically, and excellent survival can be expected in younger patients (Porter and Davis 2002). In the UK as a whole, survival has not improved to the extent hoped 30 years ago when desferrioxamine became available, and this is probably due to the problems thalassaemic patients experience in tolerating regular self-administered infusions (Modell et al 2000). However, at least in part due to more tolerable and effective regimens using oral iron chelators, there is growing evidence that life expectancy across whole populations has improved over the last 7 - 8 years (Telfer et al 2006, Borgna-Pignatti et al 2006).

Constant monitoring for complications, and their timely treatment where possible, goes hand in hand with organising regular blood transfusions and managing chelation therapy throughout the patient's lifetime. As in other chronic lifelong conditions which demand a high level of medical intervention, it is not just the technical care that affects the patient's life experience, but also the way in which that care is delivered. Provision of patient-centred services is one of the most important factors, and clinics should take particular care to minimise disruption to education, employment and family life, allowing them to live as fully and normally as possible. Such care can materially improve survival by enhancing adherence to difficult treatment regimens.

Section A

Organisation of thalassaemia services

3

Networks for Care

"There is a problem of being treated at a regional hospital where they very rarely see a thalassaemia patient and awareness is almost non-existent. One does feel isolated. It would be good if at least one doctor could take an interest in my condition!"

"My doctor is not a specialist in thalassaemia treatment and I sometimes feel he should know more."

"My doctor could do more for me by ensuring he has contact with specialist units and consultants to compare treatments. He could be better informed."

3.1 Aims

To provide specialist multi-disciplinary care to all patients, while ensuring that regular treatment is given as conveniently as possible, close to the patient's home.

To profile a service emphasizing prevention, early detection and management of complications and improved quality of life.

To provide a flexible approach to education and support of patients and families in coping with the physical, psychological and social challenges of living with thalassaemia and its treatment

To ensure good communication between patients and families, and the various agencies involved in their welfare, including the health care teams at the local Clinics and specialist Centres, social services, educational services etc.

3.2 Standards

- All regions in England should be covered by a clinical network incorporating local thalassaemia Clinics and one or more Specialised Thalassaemia Centres.
- Procedures within the network should ensure that all patients have access to a specialist Centre, either for their regular care if living nearby or for regular review at least once a year, and for additional specific consultations as needed, if living more distantly.
- The network should have sufficient resources (health care professionals, management and administrative staff) to function effectively, and should develop systems for information sharing, clinical governance, accountability and staff development.
- A 'Key Contact' health professional will be designated for each patient.
- Patients and carers should receive regular education, supervision and support in thalassaemia care, chelation therapy and other home treatments.
- Hospital admissions should be minimised by adequate monitoring, management of chelation, and early identification and treatment of complications.
- Local Clinics and specialised Centres within the network, should record and exchange information relating to clinical events monitoring investigations, and changes in treatment. Information should be shared with patients, carers and GP's.
- Patients and carers should be involved in making decisions about management and delivery of care. They should be encouraged to follow progress by receiving copies of clinical letters and recording important information in a hand-held record.
- Patients and carers should have access to peer support groups.

3.3 Rationale

The 'National Service Framework for Long-term Conditions' (DH 2005[1]) with its emphasis on supported self-care and pre-emptive interventions, is relevant for thalassaemia services. While hospital care is inevitable for transfusions and complex clinical and diagnostic interventions, most routine care, such as the administration of iron chelation and other medication, is undertaken by the family at home. Patients and families who understand fully their condition, are involved in every care decision, and are guided and supported in self-care become truly expert patients, and this helps in ensuring optimal adherence to treatment and in maximising quality of life.

The thalassaemia care team should be easily accessible, and outreach personnel should be available to make home visits to train and support families. Primary health care agencies, including health care workers at the local General Practice Health Centre, as well as community paediatric services, should be aware of the condition and its implications and potential problems.

A designated 'key contact' health professional, with whom the family will become familiar and comfortable, is essential for streamlining access to services, clinic appointments, transmitting results of investigations and troubleshooting medical and psychosocial complications as they occur.

Regular monthly transfusions are routine treatment, but if the organisation for delivery is poor and inflexible, this causes great inconvenience to the patient and family, and impairs quality of life. A well planned process is required, delivering treatment close to the patient's home or work. Many patients prefer to arrange their transfusions during the evening or overnight, in order not to interfere with school/college/work commitments.

More complex aspects of care, such as decisions about iron chelation, and management of specific complications, require specialist knowledge, experience and expertise. Opinions on best practice are changing continually, as clinical trials and studies mature and results are disseminated and discussed. All patients should benefit from specialist expertise and this requires access to a Specialised Thalassaemia Centre, providing a comprehensive range of services delivered by professionals with a particular interest in the management of the conditions. Excellent results for thalassaemia treatment have been reported from large centres in the UK (eg Porter and Davis 2002) but many patients currently do not have regular access to such centres (Modell et al 2001). We recommend that smaller local Clinics are linked with larger specialist Centres in a 'shared care' clinical network. This should bring optimal specialist input to the care of all patients, including a review visit for every patient at the Centre at least once a year. Designation of such Centres will drive up quality and efficiency through consolidating teams for the most specialised aspects of care (Children's NSF, Department of Health 2003). Clinical networks involving local clinics and specialised centres have a long track record in managing childhood leukaemia and other childhood cancers, and have been successfully developed for management of other chronic conditions in childhood such as Cystic Fibrosis (Cystic Fibrosis Trust 2001).

Communication is a key element in efficient functioning of a care network. When a patient is being treated by multiple agencies, relevant information will need to be meticulously shared to avoid omission or duplication and to optimise treatment. This is more challenging but particularly important where there are communication or language difficulties. Patient-held records can be an effective way of transmitting information between clinical staff in different clinics, and also provide an opportunity for the patient to gain a better understanding and become more involved in their own care and monitoring. A hand-held 'filofax' file has been developed for this purpose by the UK Thalassaemia Society, and is available free of charge from the UKTS office.

Collecting systematic records of all affected individuals is essential in planning, commissioning, delivering and monitoring care for long term conditions. The UK Thalassaemia Society previously supported a national register, which generated important information on disease prevalence, mortality trends, and emerging complications - for

1. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4105361

example the risk of major infection with Klebsiella species. A new DH-funded National Haemoglobinopathy Registry[1] is now being established, which will include all affected by red cell disorders, mainly thalassaemia and sickle cell disease.

3.4 Key Features

3.4.1 Communication and education

Once the diagnosis of thalassaemia is established, the parents should be offered opportunities to discuss the condition and its implications with knowledgeable and experienced health care professionals. The importance of the family as central care-givers should be emphasised. Written information should back up these discussions. It is important to check that the information is understood by the family, and when needed, to use health advocates who can communicate in the appropriate language and cultural context.

The patient's primary care team should be offered information about the condition and advised about possible acute presentations and their significance.

Charts for recording investigations, treatment changes and significant events (suggested formats are provided in Appendix A) should be maintained in the Clinic records, duplicated in the patient-held record, and sent to specialist Centre in time for the annual review visit.

Letters should be exchanged between the Clinic and Centre, with copies to the GP and to the patient/carer, at least every 6 months, after each formal annual review visit and whenever there are changes in the patient's clinical condition or treatment plan

3.4.2 Networked care

Local thalassaemia Clinics will offer regular treatment and monitoring, in such a way as to minimise the disturbance to normal everyday activities, such as schooling and work. Out of hours / weekend transfusion facilities should be available.

Specialist Centres will undertake the above role for their local population, but will have a larger team of experienced and specialised staff, under the leadership of a designated Paediatrician / Haematologist/ Paediatric Haematologist with a special interest in thalassaemia. Staff at the Centre will provide expert advice and guidance, and offer clinical consultations and specialist monitoring services.

It is expected that a specialist Centre will manage at least 20 patients on a regular basis. In some Specialised Centres there may fewer children or adults. Where this is the case, staff can gain and maintain sufficient experience if the clinics are held by Paediatric and Haematology teams working together. This has additional benefits for families in terms of continuity of care and familiarity with staff during transition from paediatrics to adult services.

Clinics where fewer patients receive their regular care should link with the nearest specialist Centre for any services they are unable to provide to the required levels. Long journeys to the specialist Centre may be unavoidable, but should be minimised by appropriate planning of investigations and clinical appointments.

Role of the local Clinic

The extent of services offered by local Clinics will vary, but it is expected that, as a minimum, they will be able to:

- provide regular transfusions at times convenient to the patient and family, and prescriptions for chelation and any other necessary therapy
- undertake regular blood tests and provision of compatible red cell units
- monitor growth, and general health and wellbeing
- organise some, or all, of the regular assessment tests
- offer support to the patient and family.

Role of the specialist Centre.

A thalassaemia Centre (in addition to the above) should:

- offer consultation at specific key 'milestones' (at diagnosis, at initiation of regular transfusion, at initiation of regular chelation therapy, at transfer to adult clinic)
- offer annual review for all the patients in the network, for overview of transfusion,

1. www.nhr.nhs.uk

chelation efficacy and side effects, and review of monitoring investigations

- supervise complex management (eg switching chelation regime, problems with adherence to chelation, decisions about splenectomy , management of endocrine, bone/joint, cardiac, liver complications and fertility treatment, bone marrow transplantation, psychosocial issues)
- guide management of acute clinical events, or take over care of such events by transfer of patient
- supervise moderate to high intensitiy surgery
- manage pregnancy
- offer education and training for staff at local Clinics and the Centre
- audit performance and outcomes
- be involved in clinical research studies

3.5 Staffing

Staffing recommendations are shown in Table 1. Key staff include one or more designated thalassaemia specialist doctors in each Centre, and a designated clinician in each local thalassaemia Clinic. In both Clinics and Centres, a 'Key Contact' (usually a nurse specialist) is required to help patients and families navigate their way around the system and support them in accessing the different services available. Both Clinics and Centres will have nursing staff working in an identified treatment area who can cannulate and supervise transfusions. Staff will need the time, as well as the expertise, to undertake the care of these patients. Precise staff numbers will depend on the number of patients being managed.

3.6 Facilities

Suitable facilities should be designated for out-patient consultation, phlebotomy and transfusions. Services should be offered at times to suit the families, and out of hours provision should always be made for routine aspects of care. The out-patient consultation area, particularly in the Centre, should enable members of the multi-disciplinary team to offer confidential consultations with patients and families. Children's out-patient and treatment areas should be separate from the general in-patient ward, and designed with the needs of the child and family in mind, providing play therapy and facilities for education and school work supervision by a hospital teacher (Children's NSF 2003).

Table 1: Staffing recommendations

		Local Clinic	Specialist Centre
Designated Consultant Paediatrician and / or Haematologist (depending on age spread of patients) providing a lead for the service. Thalassaemia will be a major interest and responsibility			✓
Designated Paediatrician and / or Haematologist (depending on age spread of patients)		✓	
Named deputy for each		✓	✓
Middle grade cover (SpR/ ST3 or above/ Staff Grade) available out of hours		✓	✓
Staff to cover the roles of:	1) Lead nurse for thalassaemia service: training, liaison, audit		✓
	2) Regular nurse(s) in ward area who can cannulate and start/supervise transfusions on day care unit, and also during evenings, overnight and week-ends	✓	✓
	3) Specialist nurse outreaching into community (responsible for home visits, teaching parents to set up desferrioxamine pump etc)		✓
	4) Key contact – could be any of above	✓	✓
	5) Identified deputy for key contact	✓	✓
Clinical psychologist with special interest, for paediatrics; Clinical psychologist for adults where available, Health psychologist if not.			✓
Access to named Psychologist		✓	
Appropriate laboratory support (transfusion and other), diagnostic imaging		✓	✓
Access to translation services		✓	✓
Access to dental team			✓
Access to Social Worker		✓	✓
Access to Dietician		✓	✓
Administrative support sufficient to ensure proper communication between patient and family/ Clinic/Centre/ GP		✓	✓
Personnel to handle patient data and input to national Registry			✓
Access to designated Cardiologist			✓
Access to designated paediatric and adult Endocrinologist			✓
Access to designated paediatric and adult Hepatologist			✓
Access to designated contact in Genetics services			✓
Access to fertility services and support from designated Obstetrician			✓
Link with bone marrow transplant service			✓

Section B

Core Management Standards

4

Initial Management of the Newly-Diagnosed Infant

4.1 Aims

To establish the correct diagnosis in an affected infant promptly, and initiate an appropriate management programme.

To ensure a good level of understanding and to minimise distress by communicating information and advice in a way which is appropriate to the culture and language of the family.

4.2 Standard

- Diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate. It should be established as soon as possible after birth, and should include genotype.
- The child must be monitored closely to determine the likely clinical course.
- The family should be informed fully and sensitively from the outset, by appropriately experienced professionals, with the use of a culturally-appropriate health advocate if necessary, and with the opportunity for full discussion. Suitable written information should be given to them.
- A management plan tailored to the individual child must be agreed and implemented.
- The family should be encouraged to give consent for the child's details to be recorded on the UK Haemoglobinopathy Registry.

4.3 Rationale

Learning that their infant has a serious blood condition inevitably comes as a shock to the parents. Parents should be aware of their risk of having an affected child through counselling during pregnancy. This counselling should have included information about inheritance, the option of pre-natal diagnosis and other choices, and the effects of thalassaemia and its treatment on the child and the family. It should be backed up by suitable written information. Additionally, if the risk was not identified during the pregnancy, affected infants may be identified through the newborn screening programme. Whenever the diagnosis is made, the way in which it is conveyed to the parents, and the initial conversations they have with professionals, will colour their expectations and attitudes. The first discussions must therefore be accurate, unhurried, considered and sensitive.

Parents will need to understand that it is not possible to predict the severity of the condition or the need for transfusions and chelation therapy from the outset, and children need to be monitored carefully for signs of poor growth, failure to thrive, complications of anaemia and bone marrow expansion - clinical features indicative of the need for regular transfusion. Genetic analysis usually, but not always, helps to predict the clinical phenotype. Routine DNA testing should therefore include β globin genotype, α globin genotype and a determinant of persistent fetal haemoglobin production (the *Xmn*1 C to T polymorphism) (Ho et al 1998).

4.4 Key interventions

4.4.1 The diagnosis should be anticipated from antenatal screening, and established by prenatal diagnosis where requested or by neonatal testing. If not, affected infants may be identified through the newborn screening programme. The baby and parents should be seen as soon as possible and preferably within two weeks. There should be no delay in referral because the child remains clinically well: important information is given, discussions take place and investigations should be instigated at this stage. If the diagnosis has not been made at these stages,

and the presentation is a clinical one, then assessment may be urgent, within one to two days.

4.4.2 For babies identified by the screening programme, an initial home visit may be preferred. Where the parents already have a relationship with a specialist nurse counsellor, from discussions in the antenatal period, s/he may be the best person to make this contact. It is important to stress the initially unpredictable clinical course for any individual child, and the range of possible needs should be covered in discussion. The nurse can then accompany the family to the first hospital consultation soon after.

4.4.3 Haematological and DNA diagnosis should be established as soon as possible by the following tests:

- Full blood count and blood film examination
- Haemoglobin analysis by electrophoresis or high performance liquid chromatography (HPLC)
- Genetic analysis for β thalassaemia mutations, α thalassaemia genotype and *Xmn*1 C-> T polymorphism

Family studies may be informative.

The parents should also be tested if results are not available from prior screening.

4.4.4 The initial clinic visit will usually be to the unit where most of the care will be provided, most often the local Clinic. Staff seeing the family may want to discuss details of the case with the Centre beforehand, and to set up an opportunity for the family to be seen at the Centre soon after. It should be emphasised that the clinical phenotype cannot be predicted accurately in the early stages, and that the child will be monitored carefully for clinical signs indicative of the need to commence transfusion. The arrangements for care should be discussed - wholly at the Centre if they live near, or based at the local Clinic if more convenient - and the plan for regular, at least annual, review at the Centre with additional contact whenever required should be explained.

4.4.5 Ample time should be given to enable parents to ask questions and clarify issues. A professional interpreter is essential at this consultation if the family are not primary English speakers. If only one parent is present, it is advisable that a friend or relative accompanies them to help them to remember afterwards what was discussed. Strenuous efforts should be made to involve both parents from the start. When both attend, it is important to be sure that each has a chance to ask his/her own questions and discuss his/her own issues.

4.4.6 Appropriate written information should be made available.[1] The family should additionally be given the contact details for the UK Thalassaemia Society and any local branches/support organisations.

4.4.7 The initial meeting is likely to be dominated by the family's need to understand the nature and implications of the child's newly diagnosed condition. Genetic counselling, with regard to options in future pregnancies, can be mentioned, but it is better to arrange a further meeting to address this issue; it must not be forgotten or eclipsed by clinical concerns about the child. At this meeting there should also be discussion of the implications of possible carrier status in siblings and other family members, who should be offered testing.

4.4.8 The parents should meet and exchange contact details with their local Key Contact staff member.

4.4.9 Arrangements should be made for the child and parents to visit the most convenient Specialist Centre as soon as possible (within six weeks), and before a red cell transfusion is given, unless transfusion is clinically urgent.

4.4.10 After the visit a written summary, covering the discussion and follow up arrangements, should be exchanged between local Clinic and Centre, and copies sent to the GP and the family.

1. Suitable materials are available (without charge) from the APoGI – Accessible Publishing of Genetic Information – website at http://www.chime.ucl.ac.uk/APoGI/

5

Decision to Start Regular Transfusions

5.1 Aims

To distinguish carefully, using clinical and DNA-based assessments, between infants with transfusion-dependent thalassaemia (thalassaemia major) and those who can maintain acceptable health and development without transfusion (thalassaemia intermedia).

To initiate transfusion therapy in thalassaemia major before the infant/child develops complications of anaemia and of bone marrow expansion.

To avoid unnecessary transfusion in thalassaemia intermedia.

5.2 Standard

- Infants with β thalassaemia will be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion will be started promptly when there is sufficient clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity.
- Infants and children with a thalassaemia intermedia phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

5.3 Rationale

> 'Good clinical judgement cannot be replaced by any kind of clear instructions regarding decisions whether to transfuse a patient'
>
> *(Loukopoulos D, Thalassaemia International Federation Conference, Palermo, October 2003)*

The decision about when to start red cell transfusions in a child with homozygous β thalassaemia is a subtle and important one. There will be some indication about likely clinical severity and likely transfusion dependency from the β globin genotype, but ultimately the decision is a clinical one. The difference between 'major' and 'intermedia' is not absolute or predictable. At a given untransfused haemoglobin level, some children apparently thrive, grow and have no clinical problems while others are plainly failing to thrive. A decision to treat cannot be made on haemoglobin level alone. In the past, some children have been transfused to the point of iron toxicity who would probably have been better without regular transfusion at all. The decision about starting transfusion must always be made by a clinician with specific experience in this area, after detailed evaluation of each child.

A decision to commence transfusion should be based on the presence of anaemia (usually below 7 g/dl) *which is accompanied by* inappropriate fatigue, poor feeding, developmental delay or regression, faltering growth, or any symptoms or signs of cardiac failure. It should be ensured that there are no correctable problems such as iron deficiency or intercurrent infection, or compounding factors such as G6PD deficiency. Into the balance should be included consideration of other factors such as age at presentation or first symptoms, increasing splenomegaly, evidence of bony expansion, changing appearance of facial bones. Sometimes there is an 'acute' anaemia, for example due to a viral infection, in a child who otherwise can maintain a satisfactory haemoglobin without regular transfusion. It is therefore reasonable to give a single transfusion initially, and then wait and reassess whether the indication for transfusion recurs. If the haemoglobin falls again promptly, it is reasonable to assume longer term dependency, and to plan for regular transfusions. Where possible, the decision to start regular transfusions should not be delayed until after the 3rd year, as the risk of developing multiple red cell antibodies increases, with subsequent difficulty in finding suitable units for transfusion.

Where transfusion is started because of fall in height velocity or bony changes (often intermedia) it should not be assumed that lifelong transfusion will then be necessary. After maximum height is achieved, and bones are fused, in some cases it is possible to 'wean off' and then stop regular transfusions entirely, although the patient still needs to be carefully monitored for other complications (see chapter 20).

5.4 Key interventions

5.4.1 After diagnosis, infants will be monitored regularly in the local Clinic and/or Centre. From the age of 4 months, these visits should be at least monthly, until the clinical phenotype is established.

5.4.2 Monitoring will include history of feeding difficulties, infections, ill health, developmental delay. Examination will include an assessment of bone expansion (including head circumference), growth curves, hepatosplenomegaly. Haemoglobin level should be checked at least monthly (see chart for infant monitoring, appendix A1).

5.4.3 The decision to initiate regular transfusion should be made by, or in consultation with, the designated clinician in the Centre.

5.4.4 Before the first transfusion, the investigations in Table 2 should be carried out. It is assumed that DNA studies have already been undertaken previously, at diagnosis, see B.4.4.3

5.4.5 Before the first transfusion, a course of hepatitis B vaccinations should be started, and completed if possible.

Table 2: Investigations prior to first transfusion

Specialty	Investigations
Haematology	Serial Hb measurements G6PD screen + assay if low
Transfusion	Full red cell phenoptype [C, c, D, E, e, K, k, Jka, Jkb, Fya, Fyb, Kpa, Kpb, MNS, Lewis]
Biochemistry	LFT and baseline ferritin assay
Microbiology	Hepatitis B surface antigen Hepatitis C antibody HIV antibody

6

Red Cell Transfusion

"When I go on the ward seeing the same nurses who know me is very reassuring."

"The best thing about my hospital is that the environment is friendly and relaxed."

"Staff should be well trained in cannulation and should realise that our veins are precious to us!"

"There is only one person at my hospital who can cannulate me and I dread him not being there."

"Everything is great now I go to a special unit but when I had treatment on the wards it was a nightmare."

"I sometimes have to wait 4 hours for my transfusion which is boring and frustrating."

"Please open the unit on evenings/weekends!"

"I would like to have my transfusions at home."

6.1 Aims

To ensure that children are transfused to an acceptable level to promote growth and well being.

To prevent complications of under-transfusion.

To ensure that transfusions are given safely and that the transfusion programme causes minimum disruption of everyday life.

6.2 Standard

- Haemoglobin levels should be maintained above 9.5-10g/dl.
- Cannulation will be undertaken by an experienced nurse or doctor.
- Pre-arranged transfusions should be started promptly.
- Good transfusion practice must be observed
- Transfusions will be given on each occasion in a designated area with suitable facilities, experienced regular named nurses and familiar supervising medical team.

6.3 Rationale

Blood transfusions, given regularly every 2-4 weeks, enable normal growth and development in childhood. A haemoglobin level maintained above 9.5-10g/dl is sufficient to inhibit bone marrow expansion and minimize transfusion iron loading (Cazzola et al 1995). The risks associated with regular transfusion include acute transfusion reactions, allo-immunisation to red cell antigens, transmission of viral infection and, in the long-term, iron overload.. Serious reactions due to misidentification can be minimized by meticulous attention to protocol in transfusion practice (BCSH Guideline 1999, BCSH Guideline 2004). Viral infections from blood are now very uncommon in the UK; however, there is always a small risk of infection from units donated during the 'window-period' of infectivity: between contracting the infection and developing the detectable antibody, or from blood-borne pathogens not currently tested for by the Blood Services.

Provision of red cell units for transfusion dependent patients requires some special considerations. Efforts must be taken to minimise the likelihood of antibody production (alloimmunisation) in these

patients. Alloimmunisation to red cells may delay the provision of blood and exposes the patients to the small additional risk of a haemolytic transfusion reaction. Transfusion red cells whose blood group profile or phenotype is matched to that of the recipient, in particular the Rh (D, C, c, E, e) and Kell (K) blood group antigens can substantially reduce the likelihood of alloimmunisation. The patient's full phenotype should be determined before transfusions are given (see B.5.4.4). The selection of red cell units which have as large a volume of red cells as possible, and are not near the end of their shelf-life, may reduce the frequency of transfusion.

For the patient and the family, the organization and efficiency of administering transfusions has a major effect on quality of life. The process includes attending for a blood sample for pre-transfusion testing, usually two to three days before the transfusion, (BCSH Guideline 2004), and then attending for the transfusion, which usually takes 4-6 hours. For blood administration, an intravenous cannula must be inserted, and this can be difficult and traumatic, particularly if the veins are hard to find. Cannulation done inexpertly increases anxiety and distress, and can damage veins, so that future access is more difficult. It is imperative to preserve the veins carefully, since the patient is dependent on life-long venous access.

Where families are able to fit in regular hospital attendances conveniently around their other activities, quality of life and motivation to adhere to treatment is enhanced. A small number of families have, at their request, been trained to supervise transfusions at home and this has continued for 8 years without any problems. This has proved very popular and convenient for those who have chosen to undertake it (Madgwick and Yardumian 1999).

6.4 Key interventions

6.4.1 The patient should be reviewed prior to each transfusion by a specialist nurse or doctor, to determine pre-transfusion haemoglobin level, to ensure that the planned transfusion is appropriate, and to discuss any problems. In the early months of treatment, the child and family should ideally be seen by the designated Paediatrician/Haematologist at every visit. Subsequently there should be a review with the designated clinician at least every 3 months in addition to the formal Annual Review visit at the specialist Centre.

6.4.2 Pre-transfusion haemoglobin level should be between 9.5 - 10 g/dl **(GRADE B)**; transfusion interval is usually between 3 and 4 weeks.

6.4.3 Red cell units which are matched for Rh (D, C, c, E, e) and Kell (K) blood group antigens should be selected.

6.4.4 Large volume units should be chosen, preferably greater than 300 mls (for adults and children when one or more full unit is required), and wheverever possible units should be less than 2 weeks old.

6.4.5 Transfusions should be given in a familiar clinical area by regular staff who are experienced in setting up and supervising transfusions. Nursing staff should be trained to site the iv cannula and set the transfusion up independently. No more than 3 attempts to site a cannula should be made by any one individual.

6.4.6 Facilities for out of hours provision are a key requirement, and become increasingly important for children of school age and beyond.

6.4.7 There should be a written transfusion policy, specifying the procedures for checking red cell units, setting up the transfusion, maximum rate and volume of transfusion, monitoring for reactions and actions to be instituted if a reaction is suspected. Staff should be aware of the policy and should be given regular training. Adherence to the policy should be audited.

6.4.8 A nurse should be in continuous attendance throughout the transfusion, at whatever time of day or night.

7

Iron Load - Monitoring and Treatment

"The worst thing about my treatment is the [desferrioxamine] injections which are very painful. An alternative treatment would be fantastic."

"I wish our hospital could provide me with … (thumb-tack type) needles as many other patients find they make taking the desferrioxamine easier."

"The home-delivered infusion pumps are fantastic!"

"The thing I would like to change about my treatment is coming off my pump and going onto an oral chelator. I have been using the pump since I was 9 years old, now I am 36…"

"I would rather have tablets than the pump; if there was one thing I could change about my treatment it would be not having to do the pump every night."

"The most helpful thing my doctor does for me is find new forms of chelation therapy"

"I would love to have combination treatment but don't know if it is appropriate for me"

7.1 Aims

To monitor body iron stores accurately, minimize body iron accumulation, and prevent tissue damage and organ dysfunction.

In patients who are already iron loaded, to reduce body iron load and minimise the toxic effects of intracellular and extracellular unbound iron.

To identify adverse side effects due to iron chelator drugs and manage them promptly.

7.2 Standards

- A protocol for iron chelation therapy in children and adults, based on current published evidence, expert opinion and local conditions should be used in the Thalassaemia Specialist Centre and local centres of the clinical network and reviewed at regular intervals.
- Chelation modalities shown to be clinically beneficial (desferrioxamine infusions, deferiprone, deferasirox, combination therapy with desferrioxamine and deferiprone) should be prescribable and recommended according to indications stated in the protocol.
- Decisions about initiating and changing chelation therapy should be made by the thalassaemia specialist, taking into account the informed preferences of the patient and carers, and other health care workers involved with the patient. Time should be taken to explain the benefits and possible adverse effects of each option, using written information in the appropriate language, and health advocacy if required. The decision process should be recorded in the patient's records.
- Patients and carers should be supported in adhering to chelation therapy using a multi-disciplinary team approach which includes clinic doctors, nurse specialists, clinical psychologists, play therapists etc. Adherence should be monitored regularly, and problems carefully identified and addressed. Patients should be encouraged

to use a treatment diary (e.g. UKTS hand-held record) to assist with monitoring.

- All patients should have access to MRI modalities (Cardiac T2* MRI and either R2 or T2* of liver) for monitoring myocardial and liver iron.
- Patients should be carefully monitored for side effects of iron chelation therapy according to the local chelation protocol, and treatment interrupted or reduced promptly to avoid serious toxicity.
- The outcomes of chelation therapy within local clinics and the network (including measures of iron status, clinical evidence of iron-related tissue damage, adverse effects of chelators and quality of life) should be audited regularly using the local protocol as an audit standard. Results of audits should be anonymised, and discussed with the thalassaemia care teams within the network and local patient interest groups and acted upon promptly.

7.3 Rationale

Background

Iron overload in thalassaemia major, if untreated, is usually fatal in the 2nd or 3rd decade of life. Toxic effects are thought to be due to the appearance of non-transferrin bound iron (NTBI) in the plasma and toxic unbound iron in intracellular compartments. These entities accumulate when the normal physiological mechanisms which sequester iron are overwhelmed. They can participate in free-radical generating reactions and are demonstrable as a labile subcomponent (Cabantchik et al 2005) or measured as total NTBI (Porter et al 1996), the latter form being particularly suited to measurements when chelators are present in the blood.

The majority of deaths, even when effective iron chelation therapy is available, are due to iron related cardiomyopathy, presenting as cardiac arrhythmias and cardiac failure. Iron toxicity also causes hypothalamic and pituitary damage resulting in growth hormone and gonadotrophin deficiency, presenting as short stature, delayed or absent puberty, and infertility. Other endocrine problems include glucose intolerance, diabetes mellitus, hypothyroidism and hypoparathyroidism. The liver is also an important site of iron toxicity: hepatic fibrosis can occur early in childhood (Angelucci et al 1995) eventually leading to cirrhosis (Aldouri et al 1987), liver failure and hepatocellular carcinoma (Borgna-Pignatti et al 2004(A)). Chronic hepatic complications are accelerated in the presence of chronic hepatitis C virus infection (Di Marco et al 2008).

There is good evidence that the majority of complications can be prevented if iron stores are maintained within a safe range and presumably (though not proven) if labile plasma and intracellular iron is suppressed. In some situations, reversal of established damage is possible if intensive iron chelation therapy is instituted and adhered to. This is well established for cardiac disease (Anderson et al 2004, Tanner et al 2008) and there are also some recent data on reversibility of endocrine dysfunction (Farmaki et al 2006).

Assessment and monitoring of iron overload

Estimating current iron stores, and monitoring their trends with time are essential for evaluating the likely risks of morbidity and mortality, and for making informed clinical decisions regarding chelation therapy. This requires knowledge of the transfusion history, and of past and present iron chelation. It is important to record dates of transfusion, the patient's weight, the volume of blood transfused at each episode and the estimated haematocrit of the transfused blood (available from the blood transfusion laboratory). These data can be used to calculate annual transfusion intensity, expressed in ml/kg/yr of pure red cells, and average daily transfusional iron loading (expressed as mg/kg/day), assuming 1 ml of pure red cells contains 1.08 mg of iron (Cohen et al 2008). Patients whose transfusion iron loading is more than 0.3 mg/kg/day, require higher doses of chelating agents to achieve negative iron balance. To assess the long-term effects of iron overload it is also necessary to know at what age chelation was started, and to ascertain the pattern of adherence to therapy and whether there have been periods of poor or absent chelation.

Serum ferritin

Serum ferritin levels (monitored serially at least every three months) are simple to do, and are a helpful guide for monitoring therapy

with desferrioxamine (DFO). Persistently high levels (>2500μg/l) are associated with an increased risk of cardiac disease and death (Olivieri et al 1994), and levels maintained in the range 500-1500 μg/l over the long term carry a relatively low risk (Borgna-Pignatti et al 2004(B), Telfer et al 2000). In the case of deferiprone (DFP) and deferasirox (DFX), levels fall concurrently with reductions of liver iron (Tanner et al 2007, Pennell et al 2006, Cappellini et al 2006) indicating effective chelation, though the prognostic significance of particular levels are not well defined. Ferritin levels are also useful in assessing the risk of DFO toxicity, and low values correlate with an increased risk of sensorineural hearing problems (Porter et al 1989). Ferritin levels are elevated during intercurrent acute infections, chronic inflammatory conditions and chronic viral hepatitis, and this leads to an overestimate of the degree of iron loading. Conversely, low levels may give a false reassurance. Long-term mean ferritin measurements on DFO in the range 500-1500 μg/l have been observed in some patients who have severe cardiac iron loading and left ventricular impairment (Tanner et al 2008). This is probably due to accumulation of iron in the myocardium either during periods of poor adherence to DFO, or in the case of older patients in the pre-DFO era, delay in starting chelation. Low vitamin C (ascorbate) levels are another cause of low serum ferritin readings in the presence of significant iron overload. Vitamin C enhances mobilization of iron from intracellular stores and is effective in increasing the efficacy of chelation with DFO. In the clinical setting, serum ferritin may rise and become more reflective of the real iron burden as the ascorbate status begins to improve and iron is effectively chelated. Measurement of vitamin C levels is possible, but now rarely done.

Liver iron

Direct measurement of liver iron, following needle or intra-operative wedge biopsy, provides an accurate measure of body iron stores (Angelucci et al 2000), however the method is invasive, iron deposition is patchy, and results show poor reproducibility, particularly if the biopsy is small or cirrhotic. Magnetic resonance imaging (MRI) is an attractive alternative for liver iron estimation since magnetic relaxation times are sensitive to tissue iron levels. The R2 (1/T2) technique (Ferriscan®) has been registered in the European Union, and can be done on a standard MRI scanner, with data sent electronically to a commercial organization for analysis (St. Pierre et al 2005). The T2* technique has the advantage that it can be done at the same time as the T2* cardiac scan (Anderson et al 2001) but is probably less accurate in measuring liver iron levels. Scanners need to be specifically set up for either R2 or T2* methodology. The two methods both appear to provide acceptable measurements of liver iron concentration over a clinically useful range of levels, when compared with chemical quantitation of liver iron (St. Pierre et al 2005, Anderson et al 2001, Wood et al 2005(B)). The optimal range of liver iron concentration for avoidance of iron toxicity and for prevention of chelator induced toxicity has not been clearly established. Although the normal level is about 0.2-1.6 mg/g dry weight (dw), there is likely to be an increased risk of chelator toxicity in thalassaemics chelated at these levels, and the lower limit of the desired range should be higher (Olivieri et al 1997). Clinical observations in genetic haemochromatosis suggest that levels between 3-7 mg/g dw should not result in hepatic or endocrine toxicity (this is the range seen in heterozygotes) (Olivieri et al 1997). Levels above 15mg/g dw in thalassaemics on DFO have been associated with an increased risk of cardiac disease (Telfer et al 2000, Brittenham et al 1994). The use of MRI scanning now enables safe, sequential assessment of liver iron, and with the current available data, it seems reasonable to aim for a level of 3-7 mg/g dw.

Cardiac MRI

Assessment of cardiac iron overload by gradient-echo T2* MRI was initially developed at the Royal Brompton Hospital in the UK (Anderson et al 2001). Gradient-echo T2* sequences are particularly sensitive to magnetic properties of tissue iron, and are acquired over a very short time span, so that motion artefacts from myocardial contractility can be minimised. There is evidence in the human heart and in an iron loaded rodent model that T2* is inversely related to myocardial iron over the clinically relevant range of tissue loading (Wood et al 2005(A), Westwood et al 2005(A)); and a

study is underway in order formally to calibrate readings against human cardiac tissue. Cardiac T2* has been shown to be reproducible on different scanners, and thus can potentially be made widely available for clinical use (Westwood et al 2005(B)). Cardiac MRI is an excellent tool for measurement of ventricular size and performance, and has highlighted an important observation that normal left ventricular (LV) ejection fraction in thalassaemia major is higher than in non-thalassaemic controls (Westwood et al 2007). There is a relationship between low T2* and impaired LV function in patients on long-term DFO chelation, LV impairment becomes increasingly likely when T2* falls below 20 milliseconds (ms) (Anderson et al 2001, Tanner et al 2006). The authors recommend 20 ms as a cut-off for early detection of cardiac iron overload. One consistent finding in cross-sectional studies of patients on long-term DFO is a lack of correlation between myocardial T2* and serum ferritin or liver iron. This is an important observation, and gives an explanation for the presence of heart disease in some patients who had been thought on standard criteria to be well chelated (Anderson et al 2001, Tanner et al 2006, Wood et al 2004). Nearly all patients with clinical evidence of heart failure have a very low T2* (<10 ms) (Tanner et al 2006, Tanner et al 2005). These findings have been confirmed in a series of studies on children in the USA and Italy (Wood et al 2004, Wood et al 2008). Cardiac T2* has also been monitored longitudinally during chelation therapy. Studies have shown improvement in T2* together with LV function in patients with cardiac dysfunction on continuous i.v. DFO (Anderson et al 2004), and in patients with low T2* (8-20 m s) treated with deferiprone-containing chelation regimes (Tanner et al 2007, Pennell et al 2006).

In conclusion, Cardiac T2* MRI is the best available method for early detection of cardiac haemosiderosis in thalassaemia. There is now sufficient evidence that T2* can be used as a surrogate marker of cardiac risk, and that T2* can be monitored during chelation therapy, enabling adjustment of chelation regime to reduce myocardial iron load, improved ventricular function and avoid clinically overt cardiac disease. It can be recommended for routine monitoring in children from 8 years of age and adults with thalassaemia (Wood et al 2008).

Iron chelating drugs

There are three chelating drugs currently licensed in the UK for treatment of iron overload in thalassaemia: Desferrioxamine (Desferal®, DFO); deferiprone (Ferriprox®, DFP) and deferasirox (Exjade®, DFX)

Desferrioxamine (DFO)

Iron chelation therapy with subcutaneous DFO infusions given 5-6 days per week over 8-12 hours and rigorously maintained has been the accepted chelation regime in thalassaemia major for over 25 years and there is a wealth of long-term clinical data on its benefits and adverse effects (Olivieri et al 1997). The only study comparing DFO chelation with no chelation was a controlled trial (not formally randomised) in 20 children, started in 1966. The treatment was 0.5 g i.m. DFO 6 days per wk, and children were followed for a mean of 5.8 years. In the treatment group there was a significantly reduced rate of liver iron loading, a stabilization of hepatic fibrosis and reduced endocrine dysfunction (Barry et al 1974). More recently, randomised controlled trials have been done comparing conventional DFO regimes with other chelating drugs (Roberts et al 2005). Follow-up studies of cohort patients have shown that long-term treatment with DFO is associated with improved survival, mainly through reduction of cardiac mortality (Olivieri et al 1994, Borgna-Pignatti et al 2004(B), Brittenham et al 1994). DFO reduces hepatic iron (Brittenham et al 1994), stabilizes or improves hepatic fibrosis (Aldouri et al 1987, Barry et al 1974) and also protects against endocrine complications (Borgna-Pignatti et al 2004(B), De Sanctis et al 2006). Despite the general positive results, some patients who are apparently adhering well with subcutaneous DFO and have low body iron stores as assessed by sequential serum ferritin levels, can still develop cardiac dysfunction due to myocardial iron toxicity (Tanner et al 2008), and endocrine complications are still observed in patients who have been chelated with DFO from an early age (Borgna-Pignatti et al 2004(B), De Sanctis et al 2006, Cunningham et al 2004). This probably reflects earlier periods of poor adherence during long-term treatment, or in older

patients, delayed initiation of chelation before DFO was accepted as standard therapy. When tissue damage is already present, intensification with continuous intravenous DFO can reverse cardiac dysfunction (Anderson et al 2004, Davis et al 2004, Davis and Porter 2000), but there is no evidence that endocrine dysfunction, once established, can be reversed with DFO monotherapy.

Adherence to DFO therapy is the major challenge now facing thalassaemic patients, their families and their carers. Quality of life studies and patient questionnaire surveys have consistently shown that regular subcutaneous infusions of DFO have a major negative impact on quality of life (Telfer et al 2005). Adherence can be improved by use of disposable pre-filled elastomeric infusers (Araujo et al 1996, Fielding and Wonke 1992) but these increase the financial cost of therapy substantially (Karnon et al 1999, Karnon et al 2008). Fine 'thumb-tack' type sub-cutaneous needles (Thalaset needles) can also help. Adherence is enhanced in childhood when the parents understand the rationale for the therapy, and feel confident in setting up the DFO infusions safely and efficiently. Additionally, it is beneficial for long-term adherence if the child takes responsibility for the infusions at an early age. It is important to offer practical support to enhance adherence wherever possible and to offer psychological support in identifying and addressing problems faced by the patient and the family which may impede adherence.

The dose of DFO must be adjusted carefully in order to maximize efficacy, while avoiding adverse side effects. In order to achieve a net reduction in liver iron concentration (and consequently a negative iron balance), doses of at least 30mg/kg 5 days per week are needed, and for adults with high transfusion requirements (equivalent to >0.5 mg/kg/day of iron intake), a dose in excess of 50mg/kg 5 days per week may be required (Cohen et al 2008). Mean doses in children should be kept between 20-30mg/kg 5 days per week, to avoid chelator toxicity. The chelation efficacy is improved by continuous intravenous infusion. Abnormalities of bone growth such as vertebral dysplasia leading to disproportionate short trunk, pseudo-rickets and genu valgum, have been described in pre-pubertal children treated with relatively large doses of DFO (>40mg/kg) and are more likely to occur in childhood when iron stores are low (De Virgiliis et al 1988). High-tone sensorineural hearing loss is also seen under these conditions, and can be predicted by calculating average daily dose of DFO/serum Ferritin >0.025 [e.g. higher risk, at ferritin 1000 μg/l, if receiving more than average of 25 mg DFO/kg/day (Porter et al 1989). Early identification of DFO toxicity, with annual checks of pure tone audiometry, and sitting and standing heights during childhood, are essential for prevention of irreversible damage (Olivieri et al 1997). Yersinia infection, presenting with fever, diarrhoea and abdominal pains, is facilitated by iron loading and DFO therapy (Lesic et al 2002). Severe and occasionally fatal Klebsiella infection has also been associated with DFO (Chung et al 2003). Patients developing high fever or signs of infection should be instructed to stop DFO chelation and seek medical advice as soon as possible

Deferiprone (DFP)

The oral iron chelating agent deferiprone, formerly known as L1, is now licensed in the European Union for adults and children over the age of 6 (although with 'limited data' concerning its use in children between the ages of 6 and 10) as a second line chelating agent. Licensed dosage is between 75 and 100mg/kg/day. There is experience, especially from South Asia in using DFP in young children as first line chelation (Lucas et al 2002, Naithani et al 2005, Choudhry et al 2004). Recently, a liquid preparation has been evaluated in young children and appears to be well tolerated and effective (El-Alfy et al, 2008 EHA Abstract 2008). There is substantial published clinical experience with use of DFP (Ceci et al 2002, Cohen et al 2000), and an accumulation of many thousand patient years of exposure. Some patients have now been taking DFP for over 10 years. Randomised, controlled studies have compared DFO with DFP monotherapy showing similar efficacy over 6 to 12 months in controlling serum ferritin and liver iron (Pennell et al 2006, Maggio et al 2002, Roberts et al 2007). Of major importance is the consistent observation in prospective randomised trials and retrospective analyses that DFP is more effective than sub-cutaneous DFO in reducing myocardial iron loading (as assessed by cardiac T2*), improving and normalizing cardiac function,

and reducing the risk of clinical cardiac events such as arrhythmia, cardiac failure and cardiac death (Anderson et al 2002, Piga et al 2003, Pepe et al 2006, Borgna-Pignatti et al 2006). Conversely liver iron may not be adequately controlled over the longer term with DFP monotherapy at 75mg/kg/day (Hoffbrand et al 1998, Tondury et al 1998, Olivieri et al 1998).

Adherence to chelation therapy is generally improved in patients switched from DFO to DFP (Roberts et al 2007, Olivieri et al 1998, Delea et al 2007), and those who find DFO infusions intolerable may have better long-term control of iron stores with DFP. However, adverse effects frequently occur. Agranulocytosis (defined as an absolute neutrophil count <0.5 x109/l) is seen in 0.5-1%, neutropenia (neutrophil count 0.5-1.5 x109/l) in 2-10%, arthropathy in 4-50% (the higher rates reported in series from the Indian sub-continent). Gastro-intestinal disturbance, intermittent elevation in ALT, zinc deficiency, and increased appetite are often reported (Naithani et al 2005, Ceci et al 2002, Maggio et al 2002, Roberts et al 2007, Hoffbrand et al 1998, Cohen et al 2003). A substantial proportion of patients have to discontinue DFP as a result of one or more of these side effects. Arthropathy is usually (but not always) reversible and in some cases, DFP can be re-introduced once symptoms have subsided. Agranulocytosis is a severe and potentially fatal complication. Most episodes occur within the first year of therapy, but cases have also been documented after several years of therapy, so continuous vigilance is required. Neutropenia episodes are characteristically mild and self-limiting, but they can be recurrent and lead into agranulocytosis, so should always be taken seriously. The manufacturers recommend that the patient is educated and reminded about the risk of agranulocytosis. In the event of a fever or signs of infection, therapy should be stopped immediately and urgent assessment undertaken including full blood count. Carrying a drug-alert card should help clinicians to act appropriately if attending a patient with this complication. Weekly monitoring of blood counts is also recommended. The finding of an association of DFP with increased liver fibrosis (Olivieri et al 1998) has not been confirmed and is not now considered a significant issue (Maggio et al 2002, Tondury et al 1998, Wanless et al 2002).

Combination therapy with DFO and DFP

There is considerable interest, and increasing clinical experience, in the use of 'combination' chelation regimes including both DFP and DFO. Wonke et al (Wonke et al 1998) showed, in a small group of patients not adequately chelated with DFO alone, a sequential regime of thrice daily oral DFP together with DFO infusions at night was feasible. This regime is more acceptable to patients, presumably because it entails fewer DFO infusions (Telfer et al 2005, Aydinok et al 2007). In randomised comparative trials and non-randomised reports, combination regimes have been shown to be as effective, or in most cases, more effective than DFO monotherapy in enhancing urinary and total iron excretion, reducing serum ferritin, and liver iron levels and improving cardiac function (Tanner et al 2007, Aydinok et al 2007, Kattamis et al 2003, Kattamis et al 2006, Mourad et al 2003, Origa et al 2005(B), Galanello et al 2006(A), Grady et al 2002). One prospective randomised trial in patients with abnormal cardiac T2* has shown a significant improvement in cardiac iron loading and cardiac function in patients on combination therapy compared to DFO monotherapy at optimal dosage (a difference of 3% in ejection fraction over one year of therapy) (Tanner et al 2007). There is also good evidence that intensive combination therapy (with daily DFP and DFO infusions initially at 40-50mg/kg at least 5x per week) is effective for reversing cardiac failure, and can be recommended as an alternative to conventional treatment with continuous intravenous DFO (Tanner et al 2008, Wu et al 2004, Porcu et al 2007). It is generally thought that endocrine complications, once established, are irreversible, but this has recently been challenged by observations of use of intensive combination chelation therapy in patients with impaired glucose tolerance (Farmaki et al 2006).

There is currently no consensus about initial dosing regimes and monitoring of therapy. Unlike monotherapy regimes of DFO or DFP, negative iron balance is usually achievable if DFO is given at least two times per week together with DFP (Grady et al 2002), but doses of DFP and DFO and

frequency of DFO infusions may need to be higher if iron loading is severe (Farmaki et al 2006, Tanner et al 2007). Dosage reductions are necessary in order to avoid chelator toxicity as iron levels drop, and it is often possible to discontinue DFO altogether whilst continuing DFP monotherapy once serum ferritin and liver iron level are consistently in the low-risk range. Adverse effects with combination therapy are common, and it is possible that the risk of agranulocytosis is increased with combination compared to DFP monotherapy (Kattamis et al 2006). The precautions concerning monotherapy with DFO and DFP should be applied with a high level of vigilance in combination therapy.

Deferasirox (DFX)

DFX is an orally active tridentate iron chelator which has a sufficiently long plasma half life in its unchelated state to enable once daily dosing. Because of its long plasma half-life and high chelator efficiency, DFX has a potential advantage over other chelator drugs in controlling the toxic component of non-transferrin bound iron. DFX differs from both DFO and DFP in that it has undergone a rigorous process of drug development culminating in well conducted Phase I, II, and III clinical trials assessing efficacy and safety, not only in thalassaemia (Cappellini et al 2006, Nisbet-Brown et al 2003, Piga et al 2006, Galanello et al 2006(B)), but also in other transfusion-dependent conditions. At the time of writing, there is on-going follow-up of trial patients for up to five years, and efficacy and safety data up to 3 years has recently been presented (Cappellini et al 2007(B), Piga et al 2007). In the pivotal Phase III trial, DFX was compared with DFO in 596 thalassaemic patients (50% under the age of 16 yrs) over the course of one year. At doses of 20 or 30 mg/kg/day, DFX was of comparable efficacy to DFO in controlling liver iron according to pre-determined criteria. At doses of 30mg/kg, neutral or negative iron balance was achieved in 82-96%, and at 20mg/kg in 47-75% of patients depending on transfusion intensity (Cohen et al 2008, Cappellini et al 2006). Long-term follow-up of trial patients up to 42 months has shown progressive decreases in serum ferritin in the majority of patients, particularly in those maintained on 30mg/kg (Cappellini et al 2007(B), Piga et al 2007). The effect on DFX on myocardial T2* and ejection fraction is not yet clear. Preliminary reports suggest an improvement in T2* but not in ejection fraction in patients with mild to moderate myocardial iron loading (Porter et al 2005, Wood et al 2007), but larger prospective studies are underway to compare cardiac parameters in groups taking DFO and DFX. At present, DFX cannot be recommended as treatment of choice for patients with cardiac iron overload, because at the time of writing there is more published evidence for clinical efficacy with alternative modalities.

Adverse effects include self-limiting skin rash (10.8%), gastro-intestinal symptoms (15.2%) and rarer reports of lens opacities, sensorineural hearing loss, drug induced hepatitis, hepatic failure, gastrointestinal ulceration, gastrointestinal haemorrhage, and renal tubular damage (See Novartis, Summary of Product Characteristics for Exjade, July 2008). One important observation is a mild dose-dependent increase in serum creatinine in 38% of patients, equivalent to a mean fall of 25% in creatinine clearance. The changes generally occur during the first 4-8 weeks of therapy and remain at a stable level during continued therapy. Intermittent proteinuria may also occur with or without changes in serum creatinine . Routine urinalysis is recommended and dose interruption considered for persistent proteinuria. In the phase III study, dose reduction was necessary in 13% of patients on DFX because of persisting changes, and the serum creatinine returned to baseline level in 25% of these (Cappellini et al 2006). The remainder continued to show mild increases, but still within the normal range for creatinine. In longer term follow-up, there does not appear to be a significant progression in renal abnormalities (Cappellini et al 2007(B), Piga et al 2007). The significance of these observations needs to be clarified. Although it is not proven that DFX causes progressive renal damage, this possibility cannot be excluded at present until longer-term follow up is available.

As expected, prospective evaluation of patient-reported outcomes in the Phase III study showed that patients were more satisfied and preferred DFX over DFO. A large majority on DFX found the once daily oral therapy convenient and were willing to continue with it (Cappellini et al 2007(A)).

The drug cost in the UK is currently very high, and it has been difficult to identify funding sources for patients who might benefit, particularly in areas of high prevalence where prescription of DFX will have a significant impact on the drug budget. Although DFX is expensive, the total comparative costs for iron chelation as assessed in a cost/utility analysis may be within the range of acceptable costs for health care intervention. Karnon et al (Karnon et al 2008) have recently estimated the incremental cost for one quality adjusted life year gained on DFX compared with DFO for a 62kg adult in the UK to be about £7770.

General considerations: Licensing and clinical guidelines

There have been significant developments in the management of iron overload in thalassaemia since the last edition of the Thalassaemia Standards. The cardiac T2* MRI technique is now widely available and is influencing management, through early detection of cardiac iron. Long-term follow-up data are consistent in showing an important cardioprotective effect of chelation with DFP. Many centres are using DFP in combination with DFO for heavily iron loaded patients. Early clinical experience with DFX is encouraging, though further follow-up is required to document the efficacy and side effect profile. It is too early to assess the cardioprotective efficacy of DFX compared to DFO and DFP.

Current licensing indications for use of chelation drugs for thalassaemia in the UK are shown in Table 3:

There are thus a range of choices to be made for each patient in optimising therapy, and opinions vary about what can best be recommended with the available (and increasing) body of evidence and expert opinion. This is reflected in differing conclusions reached in two recent publications giving recommendations about thalassaemia treatment, one by an expert committee on behalf of the Thalassaemia International Federation (Guidelines for the clinical management of thalassaemia. Second Edition ed. Nicosia: Thalassaemia International Federation; 2007), and one on behalf of the Italian Haematology Society (Angelucci et al 2008). In the Key interventions below, we have attempted to make a synthesis of the current published data which has been peer reviewed by a panel of international experts. We acknowledge that these recommendations may well change in the future when data is published on long-term clinical outcomes with different chelator drugs and regimes. The national thalassaemia registry is currently inactive, but will hopefully be in use again in some form before the next edition of these standards is published. One function of the new register will be to collate local and regional data and provide national data on outcomes including indices of chelation efficacy.

Table 3: Current licensing indications for use of chelation drugs for thalassaemia in the UK

	DFO	DFP	DFX
Children age 2-6	First line	Insufficient information	Second line if DFO contra-indicated or inadequate
Children age > 6 and adults	First line	Second line: If DFO not tolerated or ineffective	First line
Route	s.c/ i.m or i.v injection	Oral, tablet or liquid	Oral, dispersed tablet
Dosage	20-50 mg/kg 3-7 times per week. Children's dose up to 30 mg/kg	75-100 mg/kg/day	10-30 mg/kg/day
Contra-indications	Hyper-sensitivity	Pregnancy. Important teratogenic risk	Hyper-sensitivity Estimated creatinine clearance <60ml/min

7.4 Key interventions

7.4.1 General aspects of assessing and monitoring iron overload

Transfusion iron loading should be monitored by accurate recording of volume of blood transfused at each transfusion episode and using this to calculate annual transfusion volume in ml/kg of red cells.

Iron stores should be assessed regularly and systematically. Serum ferritin should be measured at least 3 monthly. MRI of liver (either R2 or T2*) every year, and additionally if significant changes to therapy occur. Cardiac T2* MRI every 2 years if T2* >20 ms, every year if T2* 10-20 ms, 6 monthly if T2*<10 ms, 3 monthly if T2*< 10 ms and any evidence of cardiac impairment. MRI monitoring should start from age 8.

The aim of therapy with all chelation regimes is to attain and maintain annual average serum ferritin at 1000 ±500 μg/l , liver iron 3-7 mg/g dry weight, and cardiac T2* >20 ms. In heavily iron loaded patients, these parameters may only be attained after several years of consistent chelation.

7.4.2 Initiating chelation

There is only one controlled trial of chelation vs no chelation, which showed a beneficial effect of i.m. DFO (Barry et al 1974), however there is plenty of long-term cohort follow-up studies in patients treated exclusively with DFO over many years. There are no randomised prospective data comparing initiation therapy with different chelation agents. DFX has been licensed as first line therapy based prospective randomised data in children, some as young as 2 years of age, nearly all of whom had previously received DFO. There is limited data on use of DFP as a first line agent, and it is not licensed for this indication.

Children <5 yrs old should be started on sub-cutaneous DFO infusions (aiming to reach 20-30 mg/kg per infusion 5-6 times per week) after receiving 10-12 transfusions, or when the serum ferritin level is consistently greater than 1000 μg/l. (Grade B)

DFX starting at 20mg/kg/day to a maximum dose of 30mg/kg/day can be used in children <6 yrs of age if DFO is not tolerated (Grade B)

DFX can be used as first line chelation in children age >6 yrs.

7.4.3 Modifying chelation

7.4.3.1 Modifying chelation in patients with acceptable iron stores

(Serum ferritin consistently 1000±500 μg/l, liver iron 3-7mg/g dry weight, Cardiac T2* >20 ms.)

There is no randomised controlled trial which specifically addresses this group of patients. DFO should still be regarded as 'gold standard therapy' and since satisfactory iron levels are being maintained, switching is not recommended.

Maintain DFO 30-50mg/kg 5-6 infusions per week (20-30 mg/kg in children) (Grade B)

Oral chelation should be considered for patients experiencing severe difficulties with adherence to DFO. DFX 20-30 mg/kg/day (Grade B) or, as second line in older children and adults, DFP 75-100mg/kg/day in three divided doses (Grade B)

7.4.3.2 Modifying chelation in patients with increasing or high iron stores and normal Cardiac T2*

(Serum ferritin consistently >1500 μg/l, and/or liver iron >7 mg/g dry weight, Cardiac T2*>20 ms.)

There is no study which specifically addresses this group of patients, however, since the aim of chelation therapy in this group is to bring serum ferritin and liver iron down to 'acceptable' levels, trials of DFO-treated patients which compare DFO with DFP, DFX or combination therapy and using ferritin and LI as end-points are relevant. There are no trials comparing DFP with DFX or switching patients currently chelating with DFP or DFX.

Patient on DFO:

Optimize dosage and adherence as far as possible (Grade B).

Consider switching to either DFX or DFP/DFO combination (both Grade B).

Patient on DFP or combined DFP/ DFO:

Increase DFP dosage up to 100mg/kg/day and/or increase frequency and dosage of DFO.

Consider switching to DFX.

Patient on DFX:

Optimize dosage and adherence to DFX (Grade B).

Consider switching to either DFO or DFO/ DFP combination.

For patients treated with DFX, it may take several years for ferritin and liver iron to reach target levels. DFX should be continued provided there is a trend to decreasing iron levels with dosage increases as required within the licensed range (20-30mg/kg/day) in increments of 5 mg/kg.

7.4.3.3 Modifying chelation in patients with increasing or high iron load, cardiac T2* not available

(Ferritin consistently >1500 μg/l, and/or liver iron >7 mg/g dry weight.)

Low T2* has been reported in more than 50% of patients on long-term DFO. Since the primary goal of chelation therapy is to prevent iron-induced cardiac disease, it is recommended that patients with evidence of high iron levels with optimization of current therapy, receive treatment which has been shown to be most effective in reducing cardiac iron loading, even if cardiac iron load cannot be assessed. This would apply to patients on DFO or DFX.

Optimize dosage and adherence with current chelation (DFO or DFX) as far as possible (Grade B).

Consider switching to combination desferrioxamine 40-50mg/kg 2-5 per week plus deferiprone 75-100mg/kg/day seven days per week (Grade B).

7.4.4.4 Modifying chelation in patients with increased cardiac iron

(Cardiac T2* <20 milliseconds.)

Recommendations can be made from two RCT's conducted in patients with myocardial T2* 8-20 ms, although the characteristics of trial patients do not fully correspond to the clinical scenarios enumerated below. In the former, DFP at a dose of 100mg/kg/day was compared with DFO at standard dosage. In the latter, combined DFO and DFP 75mg/kg/day was compared with DFO alone. DFP regimes were more effective in improving myocardial T2* and LVEF, but as a single agent, DFP was less effective than DFO in controlling serum ferritin and liver iron.

Increased cardiac iron and high body iron stores:

(Serum ferritin consistently >1500 μg/l, and/or liver iron >7 mg/g dry weight, Cardiac T2*<20 ms.)

Consider switching to combination DFO 40-50mg/kg 2-5 per week plus DFP 75-100mg/kg/day seven days per week (Grade B). The dose and frequency of DFO and dose of DFP should be determined largely by the cardiac T2* value. Intensive therapy is particularly required if T2* < 10 ms.

Increased cardiac iron and acceptable body iron stores:

(Ferritin consistently 500-1500 μg/l, and liver iron <7 mg/g dry weight.)

Consider switching to deferiprone 75-100mg/kg/day seven days per week (Grade B). The dose of DFP should be determined largely by the cardiac T2* value. Intensive therapy is particularly required if T2* < 10 ms.

7.4.4 Chelation in patients with iron-induced cardiac failure

Although in thalassaemia and other iron overload states the commonest cause of cardiac failure is uncontrolled iron overload requiring immediate revision and intensification of chelation therapy, it is very important for clinicians to be aware of other contributing and complicating co-morbidities, including infection, arrhythmia, electrolyte disturbance, renal dysfunction and poor glucose control. It is imperative for the management of decompensated cardiac failure that early input from cardiologists, preferably with experience of acute management of cardiomyopathy in general and thalassaemia in particular is sought (See Cardiac Section)

The standard therapy is continuous i.v. DFO, however, in some cases this is not accepted, not tolerated or impractical. Although there is no randomised controlled trial to compare alternative regimes, there is sufficient published experience to recommend

combination DFO and DFP therapy as an alternative. Whichever chelation option is used, cardiac function may recover relatively rapidly, but sustained compliance with an appropriate chelation regime over several years will be required for reversal of cardiomyopathy and normalization of cardiac iron levels.

Alternative options:

Continuous i.v. DFO through port-a-cath at 50-60 mg/kg/day (Grade B)

Combination DFO 40-50mg/kg s.c. infusion over 12-24 hours 5-7 per week plus DFP 75-100mg/kg/day seven days per week (Grade B). DFO can be given by continuous 24 hour i.v. infusion as an alternative to the s.c. route.

7.4.5 Additional considerations

DFO

Parents and patients should be taught how to administer subcutaneous DFO infusions. The training and performance should be documented in the patient's records. Their technique should be assessed regularly. Children should be encouraged to participate in setting up and administering the desferrioxamine infusions at an early age.

Initiation of DFO infusions in very young children (age <5) is best done starting with 2-3 infusions per week and gradually increasing to 5 infusions over a 3 month period. Means of facilitating the delivery of desferrioxamine such as Thalaset® needles, anaesthetic cream, disposable elastomeric pre-filled infuser pumps (not in very young children as the infused volumes are too large) should be offered to all children and adults

Ascorbic acid should be taken approximately 30 minutes after starting each DFO infusion.

Monitoring for adverse effects should include 3 monthly sitting and standing height, annual audiometry, and radiological investigation of any bony symptoms.

DFO should be stopped if there are symptoms of gastrointestinal disturbance (abdominal pain, severe diarrhoea) or high fever. Patients should be aware of the risk of overwhelming infection due to Yersinia and Klebsiella, and seek medical attention as soon as possible if they have symptoms or signs of severe infection

Deferiprone and combination therapy

Patients should be monitored carefully for side effects of deferiprone, with frequent blood counts (weekly counts are recommended) to detect early signs of agranulocytosis, as well as monthly liver function tests, and three monthly serum zinc levels.

Patients should be regularly reminded of the side effects of deferiprone, and should understand that if they develop fever or symptoms of infection, they should stop the medication and immediately attend for a blood count. They should carry a treatment card indicating they take deferiprone, contact details of their treating doctor, and what action should be taken if they seek medical advice after becoming unwell.

Deferasirox

Patients should be monitored carefully for side effects of deferasirox, with urinalysis, serum creatinine and liver function testing at baseline (in duplicate) and two weekly for the first month after initiation or after increasing the dosage. These tests should be done monthly thereafter. Audiometry and ophthalmology checks should be done at baseline and annually thereafter. DFX should be reduced or stopped if serum creatinine increased > 1.5 times baseline or on appearance of proteinuria.

7.5 General recommendations

Doctors and other members of the multi-disciplinary team in the Thalassaemia Specialist Centres and Local Centres of the clinical network should update themselves regularly on advances in chelation therapy.

8

Psycho-social Issues

The most helpful thing my doctor does for me is…

"… listens to what I say and is honest with me"

"… explains everything well"

"… allows me to take decisions about my treatment"

"… gives me hope and fights for me"

"A psychologist or counsellor should be part of the regular team so that we feel comfortable to go and see them on their own should the need arise."

"All staff should attempt to make patients feel as normal as possible. Be truthful. Be realistic. But, above all, be hopeful and positive about the future. Talk in practical terms about when the person will be studying, working, having homes and families of their own"

8.1 Aims

To minimise the negative impact of thalassaemia on the emotional well-being of patients.

To promote the patient's capacity for social and psychological adaptation to the condition.

8.2 Standard

- The psycho-social needs of patients growing up with thalassaemia must be considered alongside every aspect of their clinical care. This is a key role for all professionals managing the child, to be considered in each communication with the child and family.
- Core staffing of specialist thalassaemia Centres should include a Clinical Psychologist.

8.3 Rationale

It is recognised that growing up with a chronic medical condition presents significant challenges to children in accomplishing developmental tasks (Eiser 1993). Provision of psycho-social care to children should be therefore be proactive rather than reactive. It is known that a number of psychosocial factors influence patient adherence. Particular difficulties with adherence can emerge at adolescence and may require specific attention (Kyngas, et al 2000). Clinicians may also have to consider possible cultural influences on adherence, particularly where social roles are impeded by a treatment regime (Joshi 1998).

Many patients acknowledge that the way in which their regular doctors and nurses approach them, and the messages and expectations they convey in every clinical interaction, are centrally important to the way in which they think about themselves and their illness. The psychosocial wellbeing of the individual is a concern for the whole team.

8.4 Key interventions

8.4.1 Equitable access to psychology services. Patients should have the opportunity to self-refer to the psychologist. Where there are several people with thalassaemia in the same family, patients should not be required to use the same psychologist. It may also be inappropriate for parents and child to be seen by the same psychologist (particularly in the case of adolescents).

All staff working in the area should have access to training in working cross-culturally and with interpreters. They should be aware

of the variety of cultural influences on health beliefs (Helman 2002).

8.4.2 Providing information. Information should be given in a variety of formats, including verbal and written. Information may need to be provided in alternative format in the family's first language; this is not yet available for many. Information given verbally should be documented. Information should be given to children and young people at repeated points during the course of the condition, at an age appropriate level. It may also have to be given at repeated points to adult patients: particularly in the light of changes in treatment or course of the condition.

8.4.3 Child development. Regular multi-disciplinary reviews of all children, should take place, to include the Clinical Psychologist, and social worker if appropriate. Reviews should take place at defined 'milestones', and after important medical or social events

Reviews should include consideration of all aspects of the child's psychological and social development, including relationships with parents, peers and siblings, schooling issues, self esteem, identity, coping skills as well as attitude towards growing up with thalassaemia. Outcome of reviews should be documented. Where psychological or developmental problems are suspected, children/parents should be referred to clinical psychology for assessment and treatment as appropriate. Where serious psychological difficulty or psychiatric disturbance is identified, referral to specialist (tertiary) child or adult mental health services should be considered.

8.4.4 Adherence to medical regime and self-management. Information should be given to parents/patients on the options for treatment including the relative benefits or disadvantages of each option. This should include information on potential consequences of non-adherence to agreed medical treatment. Patients should be involved in decisions about treatment regimes (e.g. frequency/days off). Prescribed treatments should take into account, as far as possible, the social constraints imposed by treatment, and should incorporate some flexibility to accommodate these. All changes in treatment should be discussed with the parents/patients, and the reasons for changes made clear. Parents/patients should be involved in monitoring their progress (e.g. ferritin levels) and understanding may be enhanced if results are entered into a hand-held record. They should have the opportunity to discuss difficulties with adherence in confidence with a psychologist.

8.4.5 Supporting patients in adapting to loss and mobilising coping. Staff should be trained and supported in breaking bad news. The patient's support networks should be included where appropriate. Staff breaking bad news should remain aware of the significant impact of this on patients, and should be prepared for the range of emotional responses that may accompany this, for example anger, denial, distress. Staff should be prepared to offer support in both accepting losses associated with the bad news and in fostering realistic hope. Giving false promises should be avoided. Where appropriate, referral to the psychologist should be considered. Staff should remain alert to the possibility of depression in response to bad news, and the impact of this on motivation to adhere to medical regimes.

8.4.6 Child protection. Issues of child protection may arise in regard to a family's management of the child and his or her condition. If this is a possibility, staff should promptly seek guidance by referring to their local child protection policy or guidelines, and discussing with the lead Paediatrician for child protection.

9

Acute Clinical Presentation in the Treated Patient

9.1 Aims

To ensure that patients with thalassaemia who become acutely ill have rapid assessment and treatment, bearing in mind the range of serious complications with which they can present.

To optimise outcome after onset of a new clinical problem.

9.2 Standard

- Individual presenting to their primary care professionals, or a hospital A&E Department or clinic, with new symptoms and/or signs will be rapidly assessed by staff aware of the various acute complications which can occur in this condition.
- If staff with appropriate knowledge and experience are not available, there must be urgent consultation with members of the specialist team on site or at the Centre, and referral on after stabilisation, as necessary.
- Appropriate management should be instituted as quickly as possible.
- GPs of patients with thalassaemia should be aware of the range of acute complications thay can encounter.

9.3 Rationale

Most of the management of people with thalassaemia can take place in out-patients clinics and day care. Occasionally, however, patients present unexpectedly to their GP, clinic, or the A&E Department of their usual or any other hospital. When they do so they may be seriously ill and need prompt assessment and management, often requiring hospital admission. Assessment can be facilitated by patients carrying health records listing their diagnoses, recognised complications and recent investigation results.

While acute problems can include the same range of pathology as for any other individual, other clinical presentations occur more frequently or are of greater risk in this group and should be particularly watched for. Awareness of these, some of which are not common in a general population, will allow prompt intervention which may help towards successful outcome. General Practitioners and smaller hospital Clinics, with fewer thalassaemia patients, should contact the nearest specialist Centre if there is any concern about a patient with thalassaemia who presents acutely, or in whom the diagnosis is potentially serious or not immediately obvious.

9.4 Key interventions

Front line staff should be aware of the following possible presentations and their management.

9.4.1 Fever and infection. Splenectomised patients should have had appropriate extra immunisation against pneumococcus, and have available oral penicillin V (BCSH guidelines, Davies et al 2002). Bacterial infection is a major source of morbidity and mortality, with deaths from infection outnumbering those from iron overload for the first time in the years 2000 - 2004 (data from the UK Thalassaemia Register). Despite splenectomy, and perhaps because of successful pneumococcal prophylaxis, a majority of bacteraemias are now with gram negative organisms: Klebsiella, E Coli, sometimes salmonella species (Li et al 2001; Wanachiwanawin W 2000; Ghosh et al 2000; UK Thalassaemia Register circular 2004). Presentation is with high fever, and sometimes associated circulatory collapse, there may be evidence of pneumonia, biliary tract infection, meningitis or cerebral abcess.

A high index of suspicion, and prompt treatment with broad spectrum antibiotics such as intravenous gentamicin and piptazobactam before waiting for results of blood cultures, may reduce an otherwise high mortality risk. Where individuals have central venous catheters there is added risk of gram positive organisms, particularly Staphylococcus epidermidis; in such cases vancomycin or teicoplanin should be considered.

Yersinia enterocolitica causes infection in this patient group far in excess of others, as it thrives in high iron conditions (Cherchi et al 1995). It can cause localised infection in the tonsil or bowel, or can cause septicaemia. There is usually high fever and abdominal pain, sometimes vomiting and diarrhoea. It can be mistaken for appendicitis or other acute surgical abdomen. The organism can be cultured from blood or stool specimens. If it is suspected, all chelation treatment should be stopped until the infection is treated, or - if not confirmed - until abdominal symptoms resolve. Treatment for Yersinia is usually with ciprofloxacin, initially intravenously in an acutely ill patient; Septrin and augmentin are also reported to be effective. Antibiotic treatment should be commenced on clinical suspicion of Yersinia infection, in a chelated patient with fever and abdominal pain, pending a diagnosis.

Uncommonly, other specific transfusion transmitted infections such as hepatitis B (although not likely in vaccinated individuals), hepatitis C or rarely HIV cause the patient to present acutely and should be borne in mind.

The risk of neutropenia or agranulocytosis in patients receiving deferiprone should be borne in mind, so in such patients presenting with fever or other features of infection, an urgent FBC should be requested. Suitable broad spectrum intravenous antibiotics [as per local febrile neutropenia protocol] should be started immediately if the neutrophil count is significantly low.

9.4.2 Abdominal pain and/or jaundice may be caused by infection, but cholelithiasis is common and biliary colic or obstruction, with or without infection, should also be considered.

9.4.3 Cardiac problems. Sudden onset of dysrhythmias or decompensation of ventricular function with fulminant heart failure can cause acute presentation. The latter can present atypically, e.g. with abdominal swelling and pain from hepatic enlargement and ascites. Clinical assessment, ECG, CXR, and echocardiogram, plus 24 hour cardiac rythym tape if rythym disturbance is intermittent, should allow a diagnosis. Treatment will include diuretics and ACE inhibitors +/- inotropes, and intensive iron chelation (see chapters 7 and 13). These problems can be critical. Advice of the designated Centre Cardiologist should be sought urgently. Even if symptoms, such as palpitations or breathlessness, have resolved, hospital admission should be encouraged for urgent cardiological review as there may be a life threatening intermittent dysrrhythmia.

9.4.4 Endocrine problems should have been recognised by routine clinic screening and treated before becoming symptomatic, but occasionally cause acute presentations. Diabetic patients may present with hypo- or hyperglycaemia. Unrecognised hypothyroidism is a rare problem in a well-monitored patient. More likely is an acute presentation of hypoparathyroidism, with perioral or peripheral tingling or numbness or tetany.

9.4.5 Those who have hepatitis due to viral infection, usually complicated by iron overload, may rarely present with decompensated liver failure and hepatic coma.

9.4.6 For most presentations, desferrioxamine treatment should be continued. The exception is suspected Yersinia Enterocolitica infection, where it must be stopped and not restarted until the infection is fully resolved.

9.4.7 When acutely unwell, patients may not tolerate any degree of anaemia and should be transfused to a haemoglobin of >12 g/dl.

9.4.8 Recommended assessment for the acutely presenting patient should include the following (those starred * depending on clinical presentation):

- FBC, group and antibody screen, direct antiglobulin test, U+E, LFT, Calcium and Phosphate, Glucose, thyroid function.
- Blood cultures, urine culture, culture of stool*, CSF*
- ECG

- CXR*
- Echocardiogram*
- Ultrasound of abdomen*

9.4.9 Accident and emergency staff must contact the patient's own usual specialist team (Paediatrics and/or Haematology) - whether at the same or a different hospital - as soon as possible. This is facilitated where the patient carries some health records including key contact numbers. Even if the patient is not admitted, a copy of the A&E note should be sent to that team as soon as possible to alert them to the problem, and allow appropriate prompt follow-up.

10

Referral for Consideration of Bone Marrow Transplantation

10.1 Aim

To ensure that children and families can make properly informed choices about bone marrow transplantation as a treatment option for them.

10.2 Standard

- All families who have a child with a serious thalassaemia syndrome will be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, usually around 12 - 18 months of age.
- Referral does not depend upon the family having an available donor at the time, and discussions may inform the family's subsequent decisions on family size.
- The discussion must be with a transplant team with specific experience in transplanting for thalassaemia.

10.3 Rationale

Bone Marrow Transplantation (BMT) from HLA identical family donors is an established alternative treatment option for children with thalassaemia, and the only one which can result in cure. Results in recent years have improved with advances in supportive care and better understanding of the risks of graft rejection and graft versus host disease.

Several factors impact on the outcomes, including the adequacy of earlier chelation therapy, and the presence of liver disease as reflected by presence of hepatomegaly, and fibrosis on liver biopsy (Lucarelli and Clift 1999). Liver disease significantly worsens outcome. In a patient with no adverse risk factors (Lucarelli Class I) probability of survival and disease free survival are 93% and 91% respectively, with a transplant related mortality of 7%. If all three risk factors are present (Lucarelli Class III) survival and disease free survival fall to 79% and 58% respectively with a 10% risk of death during the procedure. The risk of transplant is least between 18 months - 3 years of age. UK results are broadly in keeping with this data (Lawson et al 2003) and in recent years if anything even better. The monitoring of uptake and success of this therapy can most easily be achieved by analysis of the existing UKCCSG BMT database; all UK transplant units provide detailed data which is regularly analysed and updated.

It is possible to tissue-type on a chorionic villus sample (CVS), and some children have been transplanted from cord blood taken from unaffected, matched sibling donors typed on a sample taken for prenatal diagnosis.

Umbilical cord cells from a younger sibling can act as a source of stem cells for transplantation. The results of using cord cells alone as a source of stem cells were initially variable, with slower engraftment and higher rejection risks, but there are increasing numbers of successful transplants reported (Locatelli et al 2003), and there is reduced risk of graft versus host disease compared to bone marrow or peripheral blood stem cell transplants. Unrelated cord and volunteer haematopoietic cell transplants have also proved feasible (Tan et al 2004) but such grafts are still regarded as having higher risks and being appropriate only under specific exceptional circumstances.

10.4 Key interventions

10.4.1 Bone marrow transplants, using marrow or cord stem cells, should be performed only in centres specifically experienced in transplants for thalassaemia.

10.4.2 Referral to such a centre should be encouraged for families of all children with thalassaemia major around the age of 12 - 18

months. It is paramount in all discussions of this treatment option to stress the usually excellent results of conventional transfusion and chelation therapy.

10.4.3 If the mother of a child with thalassaemia becomes pregnant, referral to the specialist transplant centre should be made for discussion of possible cord blood stem cell harvesting as a source for donor material for the affected child. If not already tested, the HLA type of the affected child should be established.

10.4.4 If she is undergoing prenatal diagnosis for thalassaemia, fetal HLA typing can be undertaken on the same sample. As long as the fetus does not also have homozygous β thalassaemia, cord cells should then be harvested if matched, and stored for potential transplant later.

10.4.5 In the absence of CVS typing, it is desirable to plan for cord blood to be collected at delivery of any potential sibling donor then tissue-typed, and stored if matched with the affected child, although local capability to offer this service is not currently consistent.

10.4.6 Follow up after transplant of the patient should be agreed between the bone marrow transplant centre and referring unit. Issues such as the presence of mixed chimerism and post transplant iron removal need special consideration. Most transplant centres have the facility for long-term post-transplant follow up of patients, when routine haematology care is no longer required, to monitor fertility, endocrine, cardiac and pulmonary complications.

10.4.7 It is important for transplanted individuals to be counselled that, when trying to conceive, they will pass a thalassaemic β gene to their children, and partner testing for haemoglobin disorder is essential.

11

Surgery, including Splenectomy

11.1 Aim

To ensure that surgical procedures are undertaken with minimal risk to the patient.

11.2 Standard

- Surgical procedures requiring general anaesthetic should be undertaken at, or after consultation with, the thalassaemia specialist Centre.
- Patients should be carefully assessed pre-operatively with special reference to cardiac, endocrine and metabolic disturbances which may require correction.

11.3 Rationale

Surgical procedures are often needed in thalassaemic patients. Splenectomy was often performed in the past in thalassaemia major patients with hypersplenism or with high blood requirements. Transfusion requirements could be significantly decreased by splenectomy if requirements are more than 200-220 ml red cells/kg/year assuming haematocrit of packed cells 75% (Rebulla and Modell 1991). This equates to 250-275 ml/kg/year of SAG-M, Buffy Coat Depleted Red Cells with a haematocrit of about 60%, currently supplied by the National Blood Service. Splenectomy is less commonly required nowadays in thalassaemia major children who have been transfused appropriately since early childhood, however it is sometimes still indicated. The risks of splenectomy include post-splenectomy sepsis, and guidelines exist for infection prophylaxis (Davies et al, BCSH guidelines 2002). Thrombocytosis and thrombotic complications can occur post-operatively, particularly in thalassaemia intermedia patients who are not regularly transfused.

Symptomatic gallstone disease is relatively common in thalassaemia major and intermedia, and cholecystectomy can often be done laparoscopically. Another common procedure in adult patients is hip replacement, which may be required for severe arthritis or fracture.

Acute presentations may include appendicitis, cholecystitis and fractures, particularly of the hip. Yersinia enterocolitica infection can mimic acute appendicitis, and it is extremely important to consider this diagnosis before undertaking unnecessary appendicectomy.

Any patient undergoing laparotomy should be considered for intra-operative open wedge biopsy of the liver. It is important not to miss this opportunity to stage liver disease and to assess body iron stores safely. Patients with thalassaemia major and intermedia are at increased risk of thrombosis, therefore peri-operative thromboprophylaxis should generally be given to cover major procedures.

11.4 Key interventions

11.4.1 Planned surgical procedures should be managed through close collaboration between the local Clinic, the specialist Centre team and the surgeon undertaking the procedure.

11.4.2 Preparation for planned procedures should generally include a period of optimal chelation therapy, and a detailed cardiac assessment. Patients should also have a dental check. Endocrine or metabolic disturbance should be excluded or corrected, with particular attention to management of hypocalcaemia, diabetes, and hypothyroidism.

11.4.3 A plan for peri-operative thromboprophylaxis should be discussed and decisions documented prior to the procedure.

11.4.4 Surgery in thalassaemia major patients should be undertaken with optimal

haemoglobin level (10-12 g/dl). In patients with thalassaemia intermedia, consideration should be given to a period of regular transfusion of several months before and after certain types of surgery, for example joint replacement, in order to suppress bone marrow and extra-medullary haematopoietic activity.

11.4.5 For all patients, the annual total volume (ml) of transfused red cells required should be recorded, to enable calculation of the average ml/kg received during the year. If high (see above) then splenectomy should be considered and discussed (Grade B).

11.4.6 Patients undergoing splenectomy should be informed about the risks of post-splenectomy sepsis and should receive the following vaccinations several weeks prior to the procedure (if not previously vaccinated): pneumococcal vaccine, HiB conjugate vaccine, Meningitis C conjugate vaccine. Pneumococcal vaccination requires 5-yearly lifelong booster doses. Asplenic patients should be advised to take long-term antibiotic prophylaxis, as per BCSH Guidelines (Davies et al 2002), and should carry a 'splenectomy card' if locally used. Thromboprophylaxis should be considered for those with persistently elevated platelet counts (Grade B).

11.4.7 Patients undergoing laparotomy for any reason may benefit from the additional procedures of open liver biopsy (for chemical iron estimation and histopathology), and cholecystectomy. Ultrasound examination pre-operatively will help identify gall stone disease.

12

Transition from Paediatric Care and Management of Adults

12.1 Aims

To ensure continuity of care and minimise disruption and anxiety as a child makes the necessary transfer from paediatric to adult services.

To identify and address psychosocial problems, and declining adherence to iron chelation and other therapy which may develop during adolescence and early adult life.

To ensure that optimal clinical care continues throughout adult life.

12.2 Standard

- Transfer from paediatric to adult care must be planned in advance for each individual, and timed to take into account his or her level of physical and psychological development.
- The young person will be familiar with the staff and facilities of the adult services prior to transfer.
- As far as possible management protocols and care pathways, including how to access acute care, should continue seamlessly from paediatric to adult services, but where this is not the case any differences should be highlighted and explained to the young person to avoid confusion.
- In young adults, active vigilance is required for development of clinical complications, so that appropriate management can be instituted.

12.3 Rationale

The transfer of young people from child to adult services requires special attention, as described in the Children's NSF. Evidence shows that it is generally poorly handled and that this increases the risk of deteriorating adherence to regular treatment (Anionwu and Atkin 2001). There is some evidence in chronic conditions that properly planned transition programmes result in better disease control and improved patient satisfaction.

The risks are especially high in young people with thalassaemia. Adolescents begin to challenge the need to continue the painful and disruptive routine of desferrioxamine infusions imposed on them by parents, doctors and nurses, and stop adhering as an expression of independence or rebellion. They may become more aware of the physical changes caused by thalassaemia and its treatment, and may be distressed at failure of pubertal development. Sensitive, age-appropriate, information should be available. Change of treatment routines at this vulnerable time needs to be sensitively handled.

Iron-related and other transfusion-related complications become increasingly common into adult life, especially if earlier management has not always been optimal. The emphasis of care increasingly focuses on early detection and treatment of emerging complications.

12.4 Key interventions

12.4.1 Transition should be planned well in advance of actual hand over of care, preferably starting by 13 years of age with a written transition care plan developed in collaboration between adult and children's services and the young person. The aim is to promote independence, understanding of the condition and confidence in an age-appropriate manner.

12.4.2 Timing of transfer should be based on a flexible approach that takes developmental readiness into account, and links to other social transitions such as leaving school. It should also be based on the assessment of patient's knowledge of thalassaemia and

treatment, and take into account concerns that the young person or family may have about the move to taking on adult responsibilities. In addition to healthcare needs, further education, work, leisure and other lifestyle options should be reviewed.

12.4.3 It is very important for the teenager and family to be taken by a familiar staff member, preferably their paediatric key contact, to visit the adult outpatient and day treatment areas, and introduced to the team there, before the first time they attend. As well as familiarising the young person to hospital facilities, he or she should also be made aware of local community services and local and national support organisations.

12.4.4 Preferably, some key staff will be involved in managing both children and adults. If the designated Haematologist works in both the children's and adult clinic, this will greatly enhance continuity. Otherwise, where practicable the Paediatrician or Paediatric Clinical Nurse Specialist should make arrangements to be in the clinic with the Haematologist on the first one or two occasions, and/or other key contacts from paediatrics should attend.

12.4.5 The administrative handling of the transfer should be planned in advance, to include transfer of medical, social care and other relevant records, and provision of summaries, including a patient's handheld summary if used locally. In particular, the first appointments in the adult clinic and treatment area should be organised such that the individual is immediately made to feel welcomed and included.

12.4.6 In caring for adolescents and young adults, additional attention needs to be focussed on early detection and management of systemic complications. These are the subject of Section C.

Section C

Prevention and Management of Complications

13

Cardiac Complications

13.1 Aim

To avoid symptomatic cardiac disease and prevent premature death related to cardiac disease by

- Maintaining good cardiac health by optimising thalassaemia treatment, preventing cardiac haemosiderosis, and effectively managing concurrent conditions which may affect the heart.
- Encouraging exercise and good nutrition, and offering counselling regarding smoking cessation and moderating alcohol intake.
- Early identification of cardiac haemosiderosis and / or signs of cardiac dysfunction, and instituting effective treatment to prevent symptomatic cardiac disease.
- Diagnosing overt cardiac disease promptly and providing urgent treatment to reverse dysfunction.

13.2 Standard

- A cardiologist should be identified for each clinical network, to collaborate with the haematologists in developing protocols, offering cardiac surveillance and care of patients with cardiac complications. Paediatric centres should identify a paediatric cardiologist to fulfil this role
- Patients should have a regular cardiological assessment from age 10.
- Myocardial iron should be monitored by Cardiac T2* from age 8 years. Cardiac T2* should be maintained >20 milliseconds by appropriate adjustment to chelation therapy (see chapter 7).
- Other common disorders seen in thalassaemics which can adversely affect cardiac function (e.g. hypothyroidism, hypocalcaemia, uncontrolled diabetes, acute infection, thrombosis, pulmonary hypertension) should be subject to regular monitoring and treated promptly
- Any symptoms or signs suggestive of cardiac disturbance should be taken seriously, investigations and management should be instituted urgently

13.3 Rationale

Cardiac disease due to transfusion iron overload remains the commonest cause of death in thalassaemia (Zurlo et al 1989, Borgna-Pignatti et al 2004(B), Telfer et al 2006). Effective iron chelation with desferrioxamine can reduce the risk of cardiac disease and improve survival (Borgna-Pignatti et al 2004, Olivieri et al 1994, Brittenham et al 1994). Patients who are poorly compliant with desferrioxamine and whose serum ferritin levels are generally above 2500 μg/l are more likely to develop cardiac problems (Olivieri et al 1994, Telfer et al 2000), but ferritin level is not a sufficiently sensitive predictor of sub-clinical cardiac disease (Tanner et al 2006). Cardiac arrhythmias, cardiac failure and sudden death can occur abruptly in a previously well patient, and this outcome is not restricted to those with ferritin levels above 2500 μg/l. Deaths from cardiac disease are now most commonly seen in the age range 15-30 years (Borgna-Pignatti et al 2004(B), Modell et al 2000). However, a recent publication reports that cardiac siderosis can be found in children from age 10 years (Wood et al 2008) and locally problems have been seen in children as young as eight. Regular assessments of cardiac iron are therefore recommended from age 8 years.

Over the last 5-10 years, there has been a decline in the incidence of clinically apparent cardiac disease in the UK and other European countries (Telfer et al 2006, Borgna-Pignatti et al 2006), and this is now a relatively rare complication in well chelated patients. The reason for this decline is probably multi-factorial: use of T2* MRI scanning, enabling

detection of cardiac siderosis and subclinical cardiac disease; improved chelation regimes, including better delivery systems for desferrioxamine and use of deferiprone-containing regimes; and better organization of follow-up and networking with specialised centres (Anderson et al 2001, Araujo et al 1996, Pennell et al 2006, Tanner et al 2007). Two randomised controlled trials have now shown that deferiprone (as monotherapy at a dose of 100mg/kg/day or in combination with desferrioxamine infusions) is more effective than desferrioxamine at standard dosage in reducing myocardial iron and improving left ventricular performance as assessed by cardiac T2* MRI (Pennell et al 2006, Tanner et al 2007). Deferiprone chelation was also associated with a reduction of cardiac events and deaths in a large retrospective Italian study (Borgna-Pignatti et al 2006).

Various techniques have been used to detect pre-symptomatic cardiac disease. These include echocardiography with tissue Doppler imaging (TDI) (Vogel et al 2003), MUGA scanning (Davis et al 2004), and T2* Cardiac MRI (Anderson et al 2001, Wood et al 2004, Wood et al 2008), which is now accepted as an essential tool in assessing iron overloaded thalassaemic patients, and is the only currently available technique for measuring myocardial iron content. Cardiac MRI is also an accurate technique for measuring left ventricular and right ventricular ejection fraction and cavity size during systole and diastole. Results of MRI scans are used widely for making treatment decisions, and some clinicians have commented that patients can be better motivated to adhere to chelation therapy by direct visualization of their own T2* scans. T2* levels >20 ms indicated absent cardiac iron and very low risk of cardiac disease. Levels 10-20 ms indicated moderate cardiac iron and moderate risk of cardiac disease. Levels <10 ms indicate high levels of cardiac iron and high risk of cardiac disease (Tanner et al 2006, Anderson et al 2001). Assessment of myocardial iron overload using Cardiac T2* MRI is discussed in more detail in chapter 7 of these standards.

Detailed functional assessment by digital echocardiography is the most practical means of regular long-term monitoring of ventricular size and function, and can be used for annual or more frequent follow up. ECG and Holter 24 hr ECG recordings are valuable to investigate specific symptoms, but are poor as screening tools for risk, with the sole exception of the development of RV overload in pulmonary hypertention. The ideal timing of investigation and repetition frequency is yet to be firmly established, though MRI every 2 years for high T2* patients and 6 monthly to yearly for low T2* groups seems reasonable.

Patients presenting with heart failure and/or arrhythmias need specialist cardiological evaluation, and urgent treatment. Cardiac failure is nearly always related to myocardial iron toxicity, but other factors are also important to consider, and can precipitate heart failure in an iron overloaded heart (e.g. hypothyroidism, hypocalcaemia, uncontrolled diabetes, acute infection, thrombosis, pulmonary hypertension). Treatment involves urgent and sustained intensification of chelation (see iron chelation section). Additionally, small volume transfusions need to be given at increased frequency to maintain Hb at 10g/dl, and avoid fluid overload from excessive transfusion volume. Use of diuretics, ACE inhibitors and beta blockers should follow the same principles as in other types of heart failure, and supervised by an experienced cardiologist. Similarly, arrhythmias are often, but not always, signs of severe myocardial iron toxicity, and urgent intensification of chelation is necessary. Use of anti-arrhythmic drugs and other interventions such as cardioversion and electrophysiological investigation and ablation should follow the same principles as in other clinical situations.

It remains important that thalassaemic patients are regularly assessed for evidence of cardiac disease, and this requires collaboration between the thalassaemia specialist and a cardiologist with special expertise in thalassaemic cardiac disease. The cardiologist should be experienced in managing these patients and aware of the differences in the clinical features compared to other cardiomyopathies. In the UK, the Thalassaemia Cardiac Clinic at University College Hospital, London has built up a large clinical experience over the past 10 years, which is available to cardiology units in other regions of the country.

There are several important observations to make on thalassaemic cardiac disease:

- Chest pain and palpitations are relatively common, but may not always relate to clinically significant pathology or severe iron overload.
- A variety of arrhythmias have been described. Ventricular tachycardia is a grave indicator of heart dysfunction, as in any form of cardiomyopathy and deserves urgent and expert assessment, usually including intensification of chelation. Atrial arrythmias do not always indicate severe cardiac iron toxicity and are increasingly evident in older cohorts of thalassaemia patients, who have previously undergone successful cardiac iron removal.
- The ECG commonly shows non-specific abnormalities particularly of repolarisation, in the anterior chest leads, but these are of unknown significance if long-standing and invariant.
- The ejection fraction values, as assessed by cardiac MRI or echocardiography, are significantly higher in thalassaemia patients, who, when well tend to have a "hyperdynamic" circulation compared to non-thalassaemics. This should be taken into account in assessing cardiac dysfunction and response to chelation therapy (Westwood et al, 2007)
- In contrast to most other cardiomyopathies, cardiac failure is potentially reversible with careful therapy including intensive iron chelation.
- There are often intercurrent complications which precipitate cardiac dysfunction in a patient with cardiac haemosiderosis, and these must be identified and treated urgently at the same time as managing chelation and cardiac therapy.

13.4 Key interventions

13.4.1 A designated paediatric and adult cardiologist should be identified for each thalassaemia specialist Centre. Cardiac monitoring for children under the age of 15 should be supervised by a paediatric cardiologist, and transfer to adult cardiac care should be planned in advance.

13.4.2 All patients should have access to T2* MRI scanning. Scans should be repeated every 2 years if T2* >20 ms, every year if T2* 10-20 ms, 6 monthly if T2*<10 ms, 3 monthly if T2*< 10 ms and any evidence of cardiac impairment. MRI monitoring should start from age 8 or earlier if initiation of chelation therapy has been delayed, or adherence is very poor.

13.4.3 Patients should have a regular Cardiology assessment, to include cardiac imaging and functional assessment. The frequency will depend largely on degree of iron overload, and we recommend that this is the same frequency as suggested for MRI scanning.

13.4.4 Any symptoms or signs suggestive of cardiac disease should be addressed immediately. Urgent referral to the Centre Cardiologist should be made, and if cardiac disease is thought likely, chelation therapy should be intensified. The findings, implications for prognosis, and treatment plan must be discussed in detail with the patient and the family. Support from the psychologist may be helpful in exploring treatment adherence issues.

14

Endocrine Complications

14.1 Aims

To ensure optimal growth, normal pubertal development and fertility.

To prevent thalassaemia-related diabetes, thyroid and parathyroid disturbance.

To detect and treat endocrine disturbance promptly and effectively.

14.2 Standard

- A paediatric and an adult Endocrinologist will be designated for each specialist Centre.
- Children should be monitored regularly and systematically for growth and development, from diagnosis up until the time when they have achieved full sexual maturity and final adult height.
- Deviations from expected pattern should be investigated and managed promptly. Children who are found to be growth hormone deficient should receive replacement therapy.
- Patients from age 10 should be checked annually for biochemical evidence of glucose intolerance, and from age 12 for hypothyroidism and hypoparathyroidism, and deficiencies treated appropriately.

14.3 Rationale

Endocrine deficiencies are common, potentially avoidable complications in thalassaemia. The commonest complications reported in a large Italian clinic are secondary amenorrhoea (50%), hypogonadotrophic hypogonadism (43%) and short stature (34%) (De Sanctis 2002). Iron toxicity is the most likely cause of these disorders, and may be responsible for pituitary damage even in well-chelated patients. However, it is important to consider other factors which may be contributing to a complex aetiology. For instance, desferrioxamine toxicity has been shown to cause vertebral dysplasia and truncal shortening in children given inappropriately high doses (De Virgilis et al 1988).

Once endocrine failure is established, it is generally irreversible. Short stature becomes apparent around the age of 10, and probably relates to the sensitivity of the pituitary gland to iron toxicity at a young age when total body iron burden is still relatively modest. It is not clear whether children who are well treated from early childhood can avoid this complication (De Sanctis 2002). However, there is good evidence that iron chelation therapy with desferrioxamine, when begun before the age of 10, significantly enhances the probability of attaining normal sexual development (Bronspiegel-Weintrop et al 1990).

Delayed puberty and hypogonadism are the most common endocrinological findings in iron overload. Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13, and in boys by the age of 14. Hypogonadism is defined in girls by the absence of breast development by the age of 16, and in boys by the absence of testicular enlargement (>4ml) by the age of 16 (De Sanctis 1995). Timing of hormone replacement therapy is controversial. Patients with delayed puberty may still have substantial growth potential, and excessive gonadal hormone administration may cause premature epiphyseal fusion. Guidelines exist for managing this problem, but individual cases need to be assessed, treated and monitored by a specialist Endocrinologist (Cappellini et al 2000).

In adolescence and adulthood, further endocrine complications may be seen. The most common complications reported in an Italian clinic were diabetes mellitus (18.8%), hypothyroidism (9%) and hypoparathyroidism (5%) (De Sanctis et al 2002).

These disorders require precise diagnosis, and appropriate endocrine replacement therapy.

Investigations and management in this complex and specialised area must be undertaken by an Endocrinologist with a special interest in thalassaemic problems.

14.4 Key interventions

14.4.1 Regular assessments of growth, including weight and height (standing and sitting), should be recorded every six months from diagnosis until final adult height is attained with referral to paediatric Endocrinologist if there is any concern.

14.4.2 Puberty should be systematically assessed annually from the age of 10, with referral to a paediatric Endocrinologist if there is any suspicion of delay (no pubertal changes in girls by age 13 and boys by age 14) or arrested puberty (puberty starts but then does not proceed).

14.4.3 Appropriate investigations, replacement therapy, and planned management of problems are best achieved by joint consultation between the Endocrinologist, and the thalassaemia clinician, optimally in joint clinics.

14.4.4 Evidence of faltering growth (declining centiles for height and height velocity) is often apparent around the age 8-12. This should be investigated thoroughly with consideration given to desferrioxamine toxicity, and growth hormone deficiency. A growth hormone stimulation test should be administered, and if positive, growth hormone therapy instituted (Grade B).

14.4.5 Delayed puberty should be fully investigated. Adolescents with evidence of hypogonadism should be treated with hormone replacement therapy, under guidance from the paediatric Endocrinologist.

14.4.6 Surveillance needs to continue into adult life too for patients who have no pubertal problems in their teens, in case of secondary gonadal failure, impotence or infertility.

14.4.7 Glucose intolerance should be watched for, with random glucose levels every 3-6 months, and oral glucose tolerance tests annually from puberty or from age 10 if there is a positive family history. Calcium and phosphate levels should be checked every 3-6 months from age 12 and parathyroid hormone levels measured if low. Thyroid function should be assessed at least annually from age 12. Endocrine deficiencies should be treated with standard therapy.

14.4.8 Patients with diabetes should be managed according to standard recommendations for Type 2 Diabetes (Diabetes NSF) and in conjunction with a specialist diabetes clinic. Patients with impaired glucose tolerance (Fasting glucose <7mmol/l, 140 min glucose 7-11.5 mmol/l) should be monitored for diabetic complications, receive advice concerning diet and exercise, and should intensify chelation. Although oral hypoglycaemic agents can be sufficient, some patients will need treatment with insulin. HBA_1C is unreliable after transfusion, and monitoring fructosamine levels can give an indication of glucose control.

15

Liver Complications

15.1 Aims

To preserve liver function and avoid liver damage related to viral hepatitis, iron toxicity, and adverse effects of iron chelation or other therapy.

To investigate liver abnormalities promptly, and offer effective treatment for any remediable pathology.

15.2 Standard

- Liver function tests should be monitored regularly.
- Liver iron levels should be maintained within safe limits to avoid progressive hepatic damage.
- Adjustments to chelation or other treatment should be made if liver dysfunction is associated with therapy
- Transmission of viral hepatitis by transfusion should be minimised by avoidance of transfusion in some countries outside of the UK, where blood quality control is not so rigorous. Vaccination against hepatitis B infection should be standard practice.
- Liver disease should be managed in jointly with a designated Hepatologist.
- Chronic Hepatitis C virus infection should be managed actively, including histological staging and antiviral therapy aimed at sustained viral clearance.

15.3 Rationale

Liver disease is common in thalassaemia major. Several contributory factors may co-exist, including viral hepatitis, hepatic toxicity due to iron loading of the liver parenchyma, biliary disease, and drug toxicity. The spectrum of clinical presentations includes acute and chronic hepatitis, obstructive jaundice, cholangitis, portal hypertension, hepatic insufficiency and hepatocellular carcinoma. A recent study of predominantly adult thalassaemics in North America showed cirrhotic change in 10.3%, and hepatitis C RNA positivity in 14.2% (Cunningham et al 2004). Hepatocellular carcinoma has been described predominantly in older patients (mean age 45 yrs) with hepatitis C infection (Borgna-Pignatti et al 2004). Liver disease was the cause of death in a relatively low percentage of Italian and Cypriot patients (Borgna-Pignatti et al, 2004; Telfer et al, 2006), however, viral hepatitis is highly prevalent in some countries (eg about 70% of Italian thalassaemics), and it remains to be seen whether liver disease will become an increasing cause of morbidity and mortality in these patients as they reach the age of 40-50.

Small studies of treatment for hepatitis C infection in thalassaemia with interferon-a monotherapy (Donoghue et al 1993, Di Marco et al 1997), and combination therapy with standard interferon- a and ribavirin (Telfer et al 1997) and PEG-interferon with ribavirin (Inati et al, 2005; Butensky et al, 2005), show that sustained viral clearance can be achieved in at least 40% of patients, and that already cirrhotic patients benefit from this treatment. Currently recommended treatment is with peginterferon alpha and ribavirin combination therapy, which produces the highest rates of sustained viral clearance. Duration of therapy is based on HCV genotype and interim assessments of viral load. NICE technology appraisal 75, 2004, gives comprehensive and practical guidance[1]. Ribavirin provokes haemolysis, and transfusion requirements are substantially increased during combination treatment, thus chelation needs to be intensified after completion of therapy. There is no consensus about use of deferiprone or deferasirox during antiviral therapy. In one trial, some of the patients used deferiprone during therapy, though assessment of neutropenia becomes more problematic, since both deferiprone and

1. http://www.nice.org.uk/nicemedia/pdf/TA075guidance.pdf

interferon may be causative (Telfer et al, 1997).

Hepatitis B infection is now rare among UK thalassaemia patients, probably because of exclusion of high risk donors, screening of units before transfusion, and hepatitis B vaccination in the majority of recipients.

There is evidence from post-BMT children that liver iron concentration and hepatitis C infection (antibody positivity) have a synergistic effect on progression of hepatic fibrosis, and that, in the absence of hepatitis C infection, fibrosis is only observed in those with a high liver iron concentration (>16mg/g dry weight of liver tissue). However, this observation was made over five years of follow-up in young patients, and progression to fibrosis may be more rapid in adult patients (Angelucci et al 2002) In general, liver iron levels should be kept low both in patients with and without viral hepatitis, and it is usually considered advisable to maintain levels between 2 and 7 mg/g dry weight. MRI methodology is now considered suitable for assessment and monitoring of liver iron levels without the need for serial biopsies (St Pierre et al, 2005; Anderson et al, 2001; Wood et al, 2005); liver biopsy is now undertaken predominantly for staging of virus liver damage.

Oral chelation therapy with deferiprone has been associated with hepatic toxicity. Mild elevations of transaminase levels are relatively common in patients receiving deferiprone, particularly if they are also hepatitis C antibody positive, but these are usually non-progressive, and rarely of sufficient severity to discontinue treatment (Ceci et al 2002; Cohen et al 2000). One small study of hepatic histology showed progression of hepatic fibrosis in 5 out of 14 patients treated with deferiprone for a median of 2.3 years (Olivieri et al 1998). Four of these five patients were infected with hepatitis C. Subsequent studies were unable to confirm an association between treatment with deferiprone and progression to liver fibrosis, and later publications suggest that the progressive fibrosis observed was more related to hepatic iron loading and hepatitis C infection (Wanless et al 2002, Maggio et al 2002; Tondury et al 1998). Drug-induced liver damage is an infrequent but important adverse reaction reported in association with deferasirox therapy (Cappellini et al, 2006). Liver function tests should be checked at baseline in duplicate, two weekly for the first month or after increasing dose, and thereafter monthly.

15.4 Key interventions

15.4.1 A Hepatologist should be designated for each thalassaemia specialist Centre.

15.4.2 Liver function tests and serum ferritin should be monitored every 3 months, and hepatitis virology every year. Adequate protection from hepatitis B virus should be ensured by a full course of vaccination initiated before the first transfusion, and then by serial monitoring of anti-HBs titre and 'booster' vaccination as needed.

15.4.3 Liver iron level should be maintained below 7mg/g dry weight (Grade B). Assessments of liver iron should be made by MRI (R2 or T2*) rather than liver biopsy.

15.4.4 Patients with active hepatitis C infection (HCV RNA positive) should be referred to the designated Hepatologist for further virological studies (genotype, quantitation of viral load), histological staging and decisions about management. Anti-viral therapy should be considered even if liver disease is relatively mild, in view of the interaction between hepatic iron loading and hepatitis C infection (Grade B).

15.4.5 Unexplained abnormalities of liver function tests should be investigated promptly. Liver biopsy remains the only modality able to provide a histopathological diagnosis.

15.4.6 Patients with established cirrhosis should be reviewed regularly, at least annually, by the designated Hepatologist. Surveillance for hepatocellular carcinoma (alpha fetoprotein, liver ultrasound or abdominal CT) is necessary, at least once each year, together with oesophagoscopy to examine for varices. Liver iron levels should be kept as low as possible in these patients, and anti-viral treatment should be considered if infected with hepatitis C.

16

Bone Problems

16.1 Aims

To prevent the variety of bone disorders associated with thalassaemia.

In those with established bone disease, to monitor and provide effective treatment.

16.2 Standard

- Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Bone changes related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.
- All patients should be encouraged to exercise, maintain a diet rich in calcium and vitamin D, avoid smoking and excessive alcohol consumption.
- Diagnosis of hypogonadism and other endocrinopathies should be prompt, and adequate hormone replacement therapy given.
- Teenage and adult patients will be monitored for osteoporosis.
- Established osteoporosis in adults should be treated with bisphosphonates.

16.3 Rationale

Inadequately transfused thalassaemics develop characteristic deformities of the skull and face. They are susceptible to fractures following minor trauma, and often develop dental deformities, dental malocclusion, and recurrent sinusitis due to inadequate drainage. Such problems should be managed by early referral to a specialist dental/ENT service with experience of these conditions. These problems are related to erythroid marrow expansion and are preventable by adequate blood transfusion regimes (Weatherall 2001). Asian children in the UK are particularly susceptible to vitamin D deficiency and rickets. Desferrioxamine-associated bone lesions in children include cartilaginous dysplasia of the long bones and spine, giving rise to shortening of the trunk and a 'pseudo-rickets' appearance. These changes can be prevented by using relatively low doses of desferrioxamine (15-35mg/kg) in young children. (Olivieri and Brittenham 1997)

Bone density scans in adolescents and adults with transfusion dependent thalassaemia show very high rates of osteoporosis and osteopenia (Jensen et al 1998). Low bone mass is also present in children below the age of 10 (Vogiatzi et al 2004). Short stature and maturation delay can make DEXA scan results difficult to interpret in patients under 16. Patients with low bone density are at increased risk of fracture, but it is still unclear how the fracture risk relates to the bone density as assessed by Z score, and whether bone fragility is as closely related to DEXA-scan findings as in post-menopausal women. Diminished bone density is seen in well chelated and well-transfused patients (Jensen et al 1998). There is evidence of increased bone resorption relative to formation (Voskaridou et al 2001). Risk factors include male gender, lack of spontaneous puberty in females, active hepatitis, heart disease, hypogonadism and diabetes (Anapliotou et al 1995; Jensen et al 1998, Origa et al, 2005). Plain X-ray of the hand and wrist can give useful information about sub-clinical bone disease, as well as an assessment of bone age in younger patients.

Adults may develop severe back pain with dire effects on quality of life. This may not be simply due to osteoporosis, and such symptoms have been observed in patients with milder degrees of bone loss, and in the absence of crush fractures. Other contributory factors may include disc disease, possibly related to long-term desferrioxamine toxicity, or extramedullary haematopoietic masses seen especially in those with thalassaemia intermedia. These patients need careful evaluation, usually with MR imaging

of the spine, and specialist input may be needed from an orthopaedic surgeon, rheumatologist, physiotherapist, and chronic pain specialist.

In general, patients should be given advice about increasing calcium and vitamin D intake in the diet, undertaking plenty of exercise and avoiding smoking and excessive alcohol consumption. Hormone replacement therapy is associated with less bone mineral loss (Anapliotou et al 1995). Treatment of established osteoporosis with bisphosphonate therapy has been effective, and reduces bone pain, and should be offered before major complications occur or severe pain develops (Voskaridou et al 2003; Morabito et al 2002). Intravenous pamidronate, given at 30-60 mg monthly, and oral alendronate have been shown to be effective (Morabito et al 2002; Voskaridou et al 2003,), but intravenous clodronate less so (Morabito et al 2002; Pennisi et al 2003). Zoledronic acid, given intravenously every 3 months, has more recently been demonstrated to increase mineral density in the vertebrae, although not the hip, and to reduce markers of bone resorption and bone pain - significant changes compared with placebo (Voskaridou et al 2006). It is unclear how long such therapy should continue, or at what level the treatment can be stopped. There is concern that osteonecrosis of the jaw, frequently reported in patients receiving these drugs for malignancy, may also occur in those with thalassaemia [Dr P Telfer, personal communication]. Bisphosphonates should probably not be given to those under 16 years of age since they may interfere with bone growth but are occasionally used, after assessment by a paediatric bone specialist, in younger patients who have symptoms attributable to low bone density.

16.4 Key interventions

16.4.1 Children with thalassaemia major should receive optimal transfusion to prevent excessive bone expansion (Grade B).

16.4.2 Dietary intake should be assessed and advice given to maintain an adequate intake of calcium and Vitamin D.

16.4.3 Children and adults should be encouraged to exercise regularly.

16.4.4 The recommended desferrioxamine dose in childhood should not be exceeded (Grade B).

16.4.5 Regular assessment of sitting height, and in the case of bone or joint pains, radiological investigations should be undertaken to rule out desferrioxamine-related bone disease (Grade B).

16.4.6 Hormone replacement therapy should be initiated after discussion with the Centre paediatric Endocrinologist, usually by the age of 16 if hypogonadism is present, and other endocrine derangements have been sought and corrected (Grade B).

16.4.7 Bone mineral density in the hip and spine should be measured every 18 - 24 months, more frequently if there is concern, by dual energy x-ray absorptiometry (DEXA) in all patients over 10 years of age.

16.4.8 Established osteoporosis (Z score < -2.5 in either hip or spine) should be managed with advice about diet, exercise, hormone replacement therapy, and bisphosphonate therapy in those over 16 years of age (Grade A).

16.4.9 Patients with severe back pain should be carefully evaluated with MRI scanning. They should be referred promptly for orthopaedic advice and pain management.

17

Fertility, and Management of Pregnancy

"I want to ask my doctor about the possibility of having children but my mum gets upset if I talk about it because she thinks it will be too risky for me. I would like to know how many women with thalassaemia have had babies."

17.1 Aims

To allow for discussion about fertility, and potential pregnancy, with appropriately experienced specialists at a time the patient wishes.

To optimise the chances for people who have thalassaemia to have children, if they wish.

To ensure that pregnancy in women with thalassaemia is managed so as to optimise outcomes for both mother and baby.

17.2 Standard

- Pubertal development, growth, and endocrine function will be closely monitored and prompt referral to the appropriate Endocrinologist made if there is any suspicion of problems.
- Women contemplating pregnancy will be assessed for possible risks to themselves and their babies and this evaluation up-dated as needed.
- At any time when the patient wishes she/ he should be referred to a Gynaecology (fertility) clinic with experience of thalassaemia patients, to allow discussion about treatment options. Culturally appropriate advocacy in these discussions is imperative.
- Women should be jointly managed during pregnancy by a 'Maternal Medicine' Obstetrician experienced with thalassaemia, and by their Haematologist.

17.3 Rationale

The pituitary and hypothalamus are very sensitive to iron damage, and hypogonadotrophic hypogonadism is a frequent complication. Diabetes and hypothyroidism can also impair fertility. Building a family is a key concern for patients and their extended family, and they greatly value discussion with a specialist who is able to explain realistically the options and likelihood of success, so minimising unrealistic expectations and consequent psycho-emotional problems. Induction of ovulation or spermatogenesis may be necessary, and must be undertaken by those with experience in managing patients with thalassaemia (Skordis et al 1990).

Increased risks to a woman with thalassaemia in pregnancy principally relate to

- cardiac problems (cardiomyopathy and arrhythmias), given the 40% increase in cardiac workload during pregnancy,
- the risk of accelerating cardiac dysfunction, pre-existing diabetic retinopathy or nephropathy (Jensen et al 1995).
- worsening osteoporosis
- the development of new sequelae of haemosiderosis after delivery, since iron chelation is usually halted for the duration of the pregnancy

For the baby, issues include

- the possibility of its having a major haemoglobin disorder, depending on the globin genotype of the father
- if the mother has diabetes, there is a four-fold increased risk of fetal anomaly and three-fold increase in perinatal mortality
- if ovulation induction results in a multiple pregnancy, there will be a substantially increased risk of premature delivery, growth restriction, and disability in the

infants. Specialist fertility care should minimise the risks of multiple pregnancy and ovarian hyperstimulation.

17.4 Key interventions

17.4.1 Iron chelation should be optimised from childhood, to reduce the risk of developing hypogonadotrophic hypogonadism and other endocrine disorders.

17.4.2 Where there is clinical or biochemical evidence of pubertal delay, including delayed pubertal growth, or other hormone disturbance, management by an appropriate Endocrinologist is required.

17.4.3 Early referral for discussion of fertility issues should be offered, even if not specifically requested, as some patients may hesitate to bring up the subject. This should be to a clinic experienced in treating patients with thalassaemia so that an informed and realistic discussion can take place. Input from other members of the multidisciplinary team may be helpful in this regard.

17.4.4 It is imperative that the couple is given the opportunity to discuss the risk of having a child with thalassaemia or other major haemoglobin disorder, for example sickle cell disease if the partner carries sickle cell trait. The partner must be offered a test and, if he or she carries thalassaemia or a variant haemoglobin, they should be counselled together about their options, and pre-natal diagnosis arranged if they wish. In discussing pre-natal diagnosis, the issue of incidental chromosomal disorders or other genetic conditions should also be considered. This may be particularly relevant if the marriage is consanguineous.

17.4.5 Careful pre-assessment of a woman with thalassaemia considering pregnancy is required, by an obstetrician experienced in the area, with proper discussion about possible risks (Protonotariou and Tolis 2000). A cardiology assessment with a view to assessing her fitness for pregnancy is strongly recommended, including echocardiogram, cardiac stress tests, assessment for arrythymias, and MRI quantitation of cardiac iron where available.

17.4.6 General pre-pregnancy issues need to be considered, as for any other woman:

- folic acid supplements (starting at least 3 months before conception)
- red cell antibodies
- rubella immune status
- HIV
- hepatitis C
- smoking cessation/limitation of alcohol intake
- review of any other relevant immunisations e.g. for hepatitis B, pneumovax, seasonal influenza

17.4.7 It should be remembered that couples may be infertile for reasons unrelated to thalassaemia, and a range of investigations may be necessary to establish the nature of the problem.

17.4.8 Induction of ovulation or spermatogenesis may be required for patients who have hypogonadism, and treatment in a centre with experience of such patients will minimise the risk of hyperstimulation syndromes and multiple births.

17.4.9 During pregnancy, the woman should be closely supervised by her obstetrician, cardiologist and haematologist (Tuck et al 1998). Transfusion requirements are likely to increase, and most medication should cease - particularly bisphosphonates and ACE inhibitors. It is usually advised that desferrioxamine should be withheld throughout pregnancy, although there are reports (Singer and Vichinsky 1999) that its toxicity in the second and third trimesters may be very low and that, in women who need iron chelation in pregnancy, continuing it could be considered. Folic acid is important in the pre- and early pregnancy period and penicillin should continue in those who have had splenectomy. Calcium and vitamin D supplements are particularly advisable if bone density was already reduced prior to the pregnancy.

17.4.10 The mode of delivery should be discussed in advance, taking account of any cardiac problems, and possible bone problems affecting the pelvis and suitability for vaginal delivery. Women with reduced stature are particularly likely to need delivery by caesarean section, since fetal growth is usually normal and cephalo-pelvic disproportion is therefore common.

17.4.11 The woman should be encouraged to resume her iron chelation as soon as she feels able to, after the delivery. If she is breastfeeding, desferrioxamine can be used. Deferiprone should not be recommenced until after breastfeeding ceases. For women with hypogonadotrophic hypogonadism, who required ovulation induction to achieve pregnancy, oestrogen replacement therapy should be resumed after breast feeding is finished. Prolonged breast feeding will add to the risk of worsening bone density, and calcium and vitamin D supplements, as well as other measures such as weight bearing exercise, should be continued, since bisphosphonates are contraindicated with breast feeding.

17.4.12 Women may develop new sequelae of haemosiderosis (particularly endocrine and cardiac problems) following pregnancy, and all these issues should be reviewed at an appropriately early opportunity following delivery.

Section D

Specialist Review

18

Annual Review at Specialist Thalassaemia Centre

"I would like my doctor to ensure he has contact with specialist units and consultants to compare treatments, and to be better informed"

"I am not sure if my treatment is up-to-date"

"I would like to have regular cardiology appointments and bone density scans. I would like to have combination [desferrioxamine + deferiprone chelation] treatment but don't know if I should ask about this."

"I think the doctor could give me more information about the latest developments in treatment, also I would like to be sure that all the routine tests are being carried out correctly."

"My doctor does not really help me a lot. This is a problem of being treated at a hospital that very rarely sees a thal patient."

18.1 Aim

To provide all children and adults with thalassaemia, regardless of where they live, access to a full range of specialist professionals and services at least yearly and more often if necessary, to ensure that their care is optimal.

18.2 Standard

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually at a thalassaemia Centre, with a team of health care professionals who have particular experience in the field.
- This should allow for broad discussion of treatment options, including any new information which has become available, and an individual treatment plan for the next 12 months will be confirmed.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre.

18.3 Rationale

Patients with these complex multi-system disorders require input from a range of specialist health professionals and access to a number of investigations not available everywhere. Linking smaller Clinics with larger specialist Centres, and individual case review there at least once a year, will offer all patients optimal specialist care regardless of where they live. The annual review is intended to be a detailed assessment of every aspect of the patient's treatment and condition to assess progress and identify areas where treatment could be improved.

18.4 Key interventions

18.4.1 The patient and family will usually visit the Centre for a pre-booked appointment. For some larger Clinics, a local agreement may be made for a Paediatrician and/or Haematologist from the Centre, often with a specialist nurse, to hold an outreach clinic there.

18.4.2 Communication of results between Clinic and Centre will be key to the effectiveness of these visits. To be effective, information on the individual patient's progress, growth charts, and results of monitoring tests undertaken in the preceding year, will need to be available for the review visit. Copies of completed monitoring charts (as in Appendix A), with copies of letters

from any specialist clinics attended, will give the necessary information. It will be a matter for local discussion, and will depend on availability of the different investigations, which are undertaken at the local Clinic or at the Centre. These should be planned so as to require the minimum possible number of hospital visits. Where logistically possible, investigations should be combined with the annual review visit.

18.4.3 Where test results become abnormal between annual reviews, Clinic staff are encouraged to discuss them with the Centre team to decide on the need to refer/start additional treatment.

18.4.4 At the visit, the consultation will be with the designated Paediatrician or Haematologist. Assessment will be made of progress in general and a review made of the patient's and family's knowledge of the condition. Any questions the family has about the child's condition, or treatment options, should be addressed. If possible the clinical psychologist can also be present, as part of the clinical team, and can pick up any problems identified at the same or a separate consultation.

18.4.5 There will be detailed review of current iron chelation regimen, adherence to it, and consideration of whether it can be improved in terms of tolerability and efficacy.

18.4.6 It will be ensured that prophylaxis against infection for splenectomised patients is appropriate (penicillin and vaccinations).

18.4.7 Weight, and sitting and standing height will be recorded and growth charts reviewed, and clinical examination will be undertaken with particular reference to heart, liver, spleen, pubertal status in relevant age group and any features of endocrine dysfunction.

18.4.8 It will be checked that the individual is attending the appropriate specialist clinics for his/her age and clinical status (cardiac, endocrine) and if not, referrals made.

18.4.9 For patients with a positive hepatitis C antibody test, an extra review together with the designated Hepatologist should be included or arranged, if the individual is not already under active regular follow up/ treatment at an appropriate hepatology clinic.

18.4.10 The issue of possible bone marrow transplantation should be raised, and consideration given to referral to a transplant centre (see chapter 10). Once a discussion has taken place this should be noted and it is not necessary to repeat at each visit, unless the family wish to revisit the question or new circumstances have arisen e.g. pregnancy, birth of another sibling.

18.4.11 Discussion about the family's plans for further pregnancies should be considered at intervals, with reference to their choice regarding pre-implantation genetic diagnosis, pre-natal diagnosis and testing/storage of cord blood.

18.4.12 It should be ensured that the patient/ family has access to relevant written informational material. They should know how to access the UK Thalassaemia Society and be put in touch with any local support group or organisation. Ideally they should be able to meet other families at the Centre.

18.4.13 After the visit the consultant should write a report including any problems highlighted and management changes suggested, with copies to the referring hospital, the GP and the patient/family. The patient's hand-held record, if used, can be completed at the end of the annual review visit.

19

Review of Patients Previously Treated Outside the UK

19.1 Aims

To ensure that patients starting, or returning, to use thalassaemia services in the UK can be assessed thoroughly at the outset.

To ensure that such patients and their families have a proper understanding of the condition and any complications.

To address any unidentified or unmanaged problems, and to ensure the person and family is introduced and integrated into local continuing care arrangements.

19.2 Standard

- Children and adults who have been receiving treatment outside the UK will, on arrival, be seen promptly at an established Centre and thoroughly assessed.
- Any complications which may have developed will be detected and discussed with the individual and family and management plans made accordingly.

19.3 Rationale

Thalassaemia services in many countries are of the highest quality and it is unlikely that a patient previously managed in, for example, Italy will have undetected problems. However, in some lower resource countries blood supplies may be erratic, screening of donor units may not be complete, or iron chelation may be unaffordable. It is possible therefore that the patient may have problems or complications of which they are unaware and / or which are untreated. Starting on an improved transfusion/chelation treatment regimen, and appropriate management of any complications which have not been recognised to date is likely to improve well-being and reduce morbidity and mortality.

19.4 Key interventions

19.4.1 Patients who have recently arrived in the UK may present to A&E with anaemia or infection, may be referred by their GP or may make contact through the local support organisation or another patient. They should be offered an early review with the team at the most convenient specialist Centre, with appropriate translation services available if needed.

19.4.2 A full medical history should be recorded including age at diagnosis, age at first transfusion, transfusion history including transfusion reactions, chelation history - frequency, doses, route; developmental history including puberty if relevant age, surgical procedures (in particular splenectomy), any identified endocrine problems, and all current medication.

19.4.3 A family history is important for general clinical assessment, and will help elucidate whether other family members should be screened for thalassaemia.

19.4.4 Patients should receive a full medical examination, recording height, weight, presence of thalassaemic facies or dental problems, the presence of an enlarged liver or spleen, stigmata of chronic liver disease, signs of cardiac failure, leg ulcers; stage of pubertal development and suggestion of any endocrinopathies.

19.4.5 Baseline investigations should be discussed with the patient and with their consent the assessments listed in Table 3 (overleaf) undertaken.

19.4.6 An early review visit should be planned to discuss the results of these investigations and any necessary treatment changes.

19.4.7 If hepatitis B non-immune, vaccination should be recommended.

19.4.8 It should be decided, and carefully explained to the patient and family, what the recommended arrangements for continuing care will be: either at the local Clinic with review visits at the Centre, or wholly at the Centre depending on proximity.

19.4.9 The family should be introduced to their key contact, and contact numbers exchanged.

19.4.10 As soon as possible they should be taken to visit the transfusion unit which they will be attending, and meet the staff there. If possible they should be put in touch with some other patients and families.

19.4.11 They should be given contact details for any local support groups or organisations and for the UK Thalassaemia Society.

Table 4: Assessments

Immediate investigations	FBC, blood film, haemoglobin HPLC (although may not be informative if recently transfused; family study may help)
	Serum or plasma ferritin assay
	ABO and full red cell phenotype and antibody screen. (If recently transfused, DNA studies for red cell antigens, via Reference Laboratory of National Blood Service)
	Hepatitis B & C serology to include Hep B surface antibody titre.
	HIV serology preceded by pre-test counselling.
	Full renal, liver, bone, sex hormone profiles, random glucose, TFTs, fructosamine if diabetic.
	Sample to Regional Transfusion Centre to define molecular variants (α and β globin genotype, -158 $^{G}\gamma$*Xmn*1 C>T polymorphism). Parental samples may be informative.
Other specialist assessments	Audiology
	Ophthalmology
	Bone densitometry
	Cardiac review
	Psychology review
	If diabetic, specialist diabetic clinic - arrange GTT if glucose tolerance uncertain
	If other endocrinopathies, endocrine clinic
	If hepatitis B antigen or C antibody positive, hepatology clinic
	Patient and family should be offered genetic counselling, as appropriate

Section E

Thalassaemia Intermedia

20

Management of thalassaemia intermedia, including haemoglobin E/β thalassaemia

20.1 Introduction

This section takes a broad overview of these conditions, and then looks in turn at the issues covered by preceding chapters as they apply to intermedia, compared to transfusion-dependent thalassaemia.

Where the same standards and key interventions apply, they are not repeated here; where there are differences these are highlighted. Some additional issues which particularly apply to these conditions are covered.

20.2 Aims

To maintain good health, normal growth and development, and a good quality of life throughout childhood, adolescence, and adulthood in people with thalassaemia intermedia, avoiding unnecessary treatment with regular transfusions in those with milder clinical features, but intervening with appropriate transfusion as needed.

To monitor regularly and systematically for early signs of morbidity due to chronic anaemia, iron overload and other consequences of untransfused thalassaemia.

20.3 Standards

- A comprehensive DNA diagnosis (β globin mutations, α globin genotype, *Xmn*1 polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established. Detailed consideration will be given to clinical and laboratory findings in order to reach a decision about transfusion and other treatment needs.
- Parents, carers, and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and therapeutic options available
- During the first 3-5 years of life, children suspected of having thalassaemia intermedia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy
- Children, adolescents and adults with this condition should continue to be monitored regularly, in conjunction with the specialist Centre
- Complications of thalassaemia intermedia should be minimised by anticipation, early detection, and appropriate treatment.

20.4 Rationale

Definition

The term thalassaemia intermedia is used to categorise patients with thalassaemia who do not have an absolute requirement for regular transfusions. It includes a wide spectrum of severity, from patients who only just manage without transfusions during childhood, to those who are virtually asymptomatic.

Genetics

Thalassaemia intermedia can be the result of inheritance of milder β globin gene mutations, allowing sufficient β globin chain production for some adult haemoglobin production. Additional genetic factors, such as co-inheritance of α thalassaemia, or the inheritance of a genetic determinant of enhanced fetal haemoglobin production, can also alleviate the severity of the thalassaemia. An important effect of these additional factors is to reduce the intracellular damage due to free α chains within the developing erythroblast. The clinical phenotype can usually be predicted from knowledge of the β

globin, α globin and *Xmn*1 polymorphism analysis (Table 5) but sometimes the clinical phenotype is not as predicted from genetic analysis.

Moderate/severe thalassaemia intermedia

This includes up to 10% of patients with homozygous β thalassaemia, the majority of those with Haemoglobin E/β thalassaemia and a very small proportion of those with haemoglobin H disease (α thalassaemia intermedia). At the severe end are patients who can only just manage without transfusions, but who have severe anaemia, reduced exercise tolerance, mild to moderate bone changes, hypersplenism, poor growth during childhood, and a delay in pubertal development. They are likely to develop gall-stones, extramedullary haematopoietic masses, and gradually accumulate iron, particularly in the liver, due to increased gastro-intestinal iron absorption. The majority in this group are treated with regular transfusions.

Mild thalassaemia intermedia

This group includes a small proportion of patients with homozygous β thalassaemia (usually predictable from genotype), some patients with haemoglobin E/beta thalassaemia, and the large majority of patients with haemoglobin H disease. It is important to identify this very mild group and to provide information tailored to their condition. Long-term complications can include pulmonary hypertension, hypersplenism, gall bladder disease, and chronic ankle ulceration.

Table 5: Genetic determinants of thalassaemia intermedia

Homozygote (or compound heterozygote) for mild β-mutation (such as IVS1-6 T>C, Codon 9 C>T)	
Homozygote for severe β mutation but persistence of Hb F due to:	Homozygote for *Xmn*1 polymorphism
	HPFH
	Other factors increasing HbF
Co-inheritance of β thalassaemia (heterozygote) and a thalassaemia-like Hb variant such as [these may result in a *major* or *intermedia* phenotype]	Hb E β thalassaemia
	Hb Lepore β thalassaemia
Co-inheritance of α thalassaemia mutations (homozygous α^+ or heterozygous α^0) with homozygous β thalassaemia resulting in decreased globin chain imbalance	
Co-inheritance of extra α gene(s) with heterozygous β thalassaemia resulting in increased globin chain imbalance	
Inheritance of a 'dominant thalassaemia' mutation (hyperunstable β globin variant)	

Specific clinical considerations

The key issue of deciding whether to start a child on regular transfusion is covered in chapter 5. Acute anaemic episodes occur in children with thalassaemia intermedia and are not necessarily an indication for long-term transfusion. Such episodes may be caused by parvovirus infection, but are more commonly associated with other viral or atypical infections, and acute haemolysis may also be exacerbated by G6PD-deficiency. Relative folate deficiency may occur and folic acid supplements are recommended (Cappellini 2000). Red cell allo-immunization is more frequent in thalassaemia intermedia (Spanos et al 1990), so providing phenotype matched units for transfusion is mandatory.

Bone marrow expansion may cause malformation of facial bones, difficulty hearing or chewing and increased sinus infections. Bone pain and pathological fracture of long bones may occur.

Untransfused patients tend to develop hepatic iron overload as a result of increased gut iron absorption. However, it is easier to achieve negative iron balance in thalassaemia intermedia, because the rate of iron loading from the gut is much less than from regular transfusions. The serum ferritin is unreliable in thalassaemia intermedia, and tends to underestimate the degree of liver iron loading.

Iron -related cardiomyopathy is unusual in children and young adults.

Particular psychosocial issues have been identified in thalassaemia intermedia patients and their families, particularly around the areas of uncertainty and anxiety about the condition, and chronic ill health (Ratip et al 1995).

Standard treatment for these patients has been splenectomy, if the spleen is large, and avoidance of regular transfusion. Doctors and patients may try to avoid transfusion dependence because of the increased burden of treatment with regular transfusions and iron chelation, the increased risk of death associated with thalassaemia major as a result of iron overload, and/or unwillingness to accept the diagnosis of thalassaemia. However, with current advances in chelation therapy and improved survival seen in thalassaemia major, and the enhanced quality of life which may accompany conversion to regular transfusions, the pros and cons of regular transfusion need to be weighed up and discussed with the family in each individual case. Indications for splenectomy include massive splenomegaly and hypersplenism. Many patients with lesser degrees of splenomegaly do benefit, with an improvement in haemoglobin level and a reduction in ineffective erythropoiesis so that transfusion dependence is delayed or averted. Removing the spleen can also improve growth velocity and pubertal development. However, the benefit is not always dramatic, and many will still eventually require regular transfusion (Fiorelli et al 1988). This variability is also seen in Haemoglobin E/beta thalassaemia (Hathirat et al 1989). Risks of splenectomy in thalassaemia intermedia include a marked thrombocytosis, post-splenectomy sepsis (Pinna 1988), pulmonary hypertension, and possibly enhanced iron deposition in the liver. The risk of thrombosis, already increased in thalassaemia intermedia (Borgna-Pignatti 1998) is further increased after splenectomy (Cappellini 2000).

Pulmonary hypertension is prevalent in untransfused adults (23%), particularly those who have been splenectomised, whereas it is rare in fully transfused thalassaemia major. Regularly transfused patients have a higher prevalence of left ventricular dysfunction and resulting heart failure, but pulmonary hypertension can itself lead to right heart failure, in slightly older intermedia patients (Aessopos et al 1997, Aessopos et al 2005). The aetiology is unclear. There is evidence from autopsy for recurrent pulmonary vascular occlusion with thrombi (Sonakul et al 1988). Hypercoagulability, thrombocytosis and increased platelet activation may be involved, and nitric oxide depletion through scavenging by free plasma haemoglobin may also play a role, as in sickle cell disease (Reiter et al 2002). Optimal management for this complication is not yet established. Aspirin therapy reduces hypoxaemia in the majority of cases (Fucharoen et al 1981). Regular transfusion is likely to be beneficial. The role of hydroxyurea, phosphodiesterase inhibitors or nitric oxide donors/analogues need further investigation.

Children and adolescents with thalassaemia intermedia are less likely than those with thalassaemia major to have short stature due to growth hormone deficiency, hypogonadism due to gonadotrophin deficiency, and other iron-related endocrinopathies. Short stature and delayed puberty are more commonly due to chronic anaemia, hypersplenism and energy deficit due to hypermetabolism. Bone age is often significantly delayed.

Asymptomatic paravertabral masses are commonly observed on routine chest X-rays, and chest or abdominal scans. Masses causing spinal cord compression, root compression, or pressure symptoms in other anatomical sites require urgent management (Dore 1992). The optimal treatment modality is not established. Radiotherapy can induce rapid resolution of pressure effects (Issaragrisil et al 1981). Goods results, although generally slower in onset, have been described with hypertransfusion and hydroxycarbamide/ hydroxyurea (Saxon et al 1998).

An additional therapeutic option for patients with thalassaemia is hydroxycarbamide. This is a cytotoxic agent which can suppress erythropoietic activity and enhance fetal haemoglobin production. The potential clinical benefits include alleviation of symptoms of anaemia, reduction in clinical jaundice because of decreased haemolysis, relief of bone pain, reduction in bone marrow and spleen enlargement and regression of extramedullary masses. In general, the clinical experience and results published in case series

have been disappointing, although response is variable. Encouraging results have been reported for specific genotypes, notably those with haemoglobin E/beta thalassaemia (Fucharoen et al 1996), Haemoglobin Lepore, and in some Middle Eastern patients (Bradai et al 2003, 2007, Alebouyeh et al 2004, Yavarian et al 2004). Better results are also expected in patients who are homozygous for the Xmn1 polymorphism, which confers enhanced fetal haemoglobin production (Alebouyeh et al 2004), or who have been splenectomised (Bradai 2007). Some patients are particularly sensitive to bone marrow suppression and become leucopenic with relatively modest doses, and too high a dose may suppress erythropoiesis rather than enhance haemoglobin levels.

Since many patients with moderate/severe thalassaemia intermedia have relatively poor quality of life, and many will eventually require transfusions and chelation therapy, allergenic bone marrow transplant should not be ruled out. The decision whether or not to pursue this option is especially difficult given the established risks of the procedure, the improving outlook for those managed with transfusions and chelation therapy, and the difficulty in predicting the long-term consequences of thalassaemia intermedia in a young child. The discussion requires careful counselling, accurate and consistent information, and good communication between the family, the Transplant Centre and thalassaemia team.

20.5 Key interventions

20.5.1 Organization of services for thalassaemia intermedia: the same considerations broadly apply to thalassaemia intermedia as for thalassaemia major, although since intermedia is relatively rare, and presents difficult management problems which cannot be easily protocolised, input from the Centre is especially important.

20.5.2 Patients should receive regular folic acid supplementation.

20.5.3 After transfusion for an episode of acute anaemia, for example after infection, the patient should be observed carefully for several months to determine steady-state symptomatology and haemoglobin level.

20.5.4 The decision for regular transfusions should be made in collaboration with the specialist Centre. Indications for long-term transfusions include symptomatic anaemia, falling growth velocity, delayed puberty, bone problems (facial deformities, recurrent fractures, premature epiphyseal fusion), pulmonary hypertension, symptomatic extramedullary haematopoietic masses, chronic ankle ulceration.

20.5.5 The rationale for transfusion should be carefully discussed with the patient and/or parents and family, perhaps over the course of several clinic visits. This will entail accepting the reality of a chronic condition in an older child, and preparing for the problems association with regular transfusion.

20.5.6 Red cell units transfused must be phenotype compatible, and matched for ABO, Rhesus (C/c,D,E/e) and Kell.

20.5.7 Assessment of iron stores should take into account the severity of the anaemia, number of transfusions received, and clinical evidence of iron-related toxicity (heart, liver and endocrine disease).

20.5.8 As the serum ferritin is unreliable in thalassaemia intermedia, an additional measure of iron stores should be undertaken; this will usually be by a non-invasive MRI technique.

20.5.9 Chelation regimes for untransfused children and young adults can be less intense than in thalassaemia major. The choice of chelator drugs is as for thalassaemia major, depending on the degree of iron demonstrated in the heart and / or liver. Desferrioxamine remains the chelator of choice for these patients. There is limited experience with deferiprone, which seems to be beneficial in Hb E thalassaemia. The efficacy and adverse effects of deferasirox in thalassaemia intermedia are not yet known. This is the subject of an ongoing clinical trial.

20.5.10 Careful consideration should be given to the risks/benefits of splenectomy in these patients. The decision must be made after consultation with the Centre, and requires careful counselling and discussion.

20.5.11 Patients with thalassaemia intermedia should be transfused for several months prior to splenectomy to reduce spleen size, suppress marrow activity, and reduce the

numbers of circulating, pro-thrombotic thalassaemic red cells.

20.5.12 Prior to the procedure, an abdominal ultrasound scan should be done to detect gall stones. If present, a cholecystectomy should also be considered. A wedge liver biopsy should be taken at the time of laparotomy, for histological assessment and analysis of liver iron content.

20.5.14 Thalassaemia intermedia patients should have regular echocardiography from age 15. Where echocardiography proves inconclusive in regard to pulmonary pressures, further investigation with cardiac MRI and right heart catheter studies should be considered to confirm the diagnosis.

20.5.15 If pulmonary hypertension is found, treatment with regular transfusion should be strongly considered. Support should be given to clinical trials in these areas.

20.5.16 Growth and pubertal development should be monitored regularly from the age of 10, and referral to the designated endocrinologist made if abnormalities are documented.

20.5.17 A period of regular transfusion during the years of peack potential growth and puberty should be considered.

20.5.18 Symptoms due to extra-medullary haematopoietic masses should be investigated, usually with MRI imaging, and treated. Radiotherapy can be considered if there is urgent need to reduce the mass; hypertransfusion and hydroxycarbamide act more slowly. Asymptomatic masses may require therapy depending on their position (eg if impinging on the spinal cord), but if not threatening vital structures, may simply be monitored.

20.5.19 Hydroxycarbamide therapy should be instituted only after careful definition of the expected benefits. The decision should be made with the Centre physician. The patient should be made fully aware of possible adverse effects of the drug, and supplied with written information. It should be started at a dose of 10-15 mg/kg/day, and the full blood count monitored frequently. The maximal dose is not known, but it is unlikely that patients will tolerate doses in excess of 20-25 mg/kg/day.

20.5.20 Referral to a bone marrow transplant centre, with specific experience of transplanting for thalassaemia, should be offered to families, for detailed discussion of transplant as an option.

20.5.21 Patients with moderate/severe thalassaemia intermedia should be reviewed at least annually at the specialist Centre.

20.5.22 Suggestions for regular monitoring tests, (which differ in some respects from those for thalassaemia major) are given in Table 6.

Table 6: Suggested monitoring for untransfused thalassaemia intermedia patients, after age 3

	Frequency	Age at start
Clinical examination to include:	3 monthly	Age 3
Height		
Weight		
Spleen size		
Liver size		
Assessment of facial bone deformity and dental state		
Pubertal development	6 monthly	Age 10
Cardiac assessment	5 yearly, or more frequently if abnormal	Age 15
Blood tests	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	Age 3
FBC		
Liver function, renal function, urate		
Ferritin		
DEXA bone density	5 yearly	Age 15
ECHO, including assessment for pulmonary hypertension (Tricuspid jet velocity should be quoted)	5 yearly, or more frequently if abnormal	Age 15
Formal assessment of body iron stores/MRI if available	5 yearly or more frequently if abnormal	Age 15

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Appendices

A

Suggested Formats for Charts for Recording Investigations, Treatment Changes and Significant Events

Notes

- Standard "centile charts" for monitoring height and weight, and head circumference in infants should be maintained.
- Many Centres will have developed their own monitoring charts. The following are included for use if preferred. Minimum key information which must be recorded, in whatever format, and reviewed systematically, includes pre-transfusion Hb levels, transfusion dates and volumes given [with annual mls / kg calculated] and specific tests monitoring for chelator efficacy and adverse effects.
- Each is intended to be used for a 12 month period (year stated at top), starting new sheets each January.

A.1 Monitoring chart for children up to 3 years of age

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Date	Height cm	Weight kg	Head circum-ference	Hb level g/dl	Ferritin ng/ml	Liver function tests#	Spleen size cm	Transfusion (ml)/date	Comments

record 'n' (normal) or include abnormal results

Total ml transfused this year:	
/ mid-year wt (kg):	
= Red cell transfusions - ml/kg for this year:	

Date	Vaccinations given:

A.2 Transfusion Record and 3 monthly monitoring (from age 3)

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Date	Pre-Tx Hb g/dl	Mls transfused	Ferritin* ng/ml	LFT*#	Glucose* mmol/l	Calcium* µmol/l	Comments

** usually 3 monthly* *# record 'n' (normal) or include abnormal results*

Total ml transfused this year:	
/ mid-year wt (kg):	
= Red cell transfusions - ml/kg for this year:	

Any transfusion reactions	
Date	**Reaction type**

A.3 Chelation Record

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Regimen	**Date**	**Desferrioxamine**				**Other chelator**			**Comments**
		Dose	**Route**	**Frequency**	**Delivery device**	**Name**	**Dose**	**Frequency**	
Usual regimen (start of year)									
Change in regimen:									

NOTE! Monitor and record weekly FBC if taking deferiprone

Date	**N – Normal, or record result if not**
...	...

NOTE! Monitor and record urinalysis and U&E if taking deferasirox

Date	**Urinalysis**	**Urea / creatinine**
Baseline		
...	...	...

A.4 Yearly Monitoring Summary (from age 3)

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Date of annual review:		Transfusion interval:	
Height:		Transfusion volume [mls / kg mid-year weight] in last year	
Weight:			

:

Start at age (yrs)	Investigation/ measurement	Date of investigation (where applicable)	Undertaken at		Result	,	Comments
			Clinic	Centre			
3	**Growth**				Height progressing along satisfactory centile		
					Growth velocity unsatisfactory		
3	**Physical examination**				Bone changes		
					Hepatomegaly		
					Splenomegaly		
					Other:		
3	**Average Hb (pre-transfusion)**				<9.5 g/dl		
					9.5-10.5 g/dl		
					>10.5 g/dl		
3	**Average serum Ferritin**				<1000		
					1000-2500		
					>2500		
3	**Serum creatinine**				Normal		
					Change < 2 x baseline		
					Change > 2 x baseline at any point		
3	**Liver function tests (over last 12 months)**				Transaminases >2x upper limit of normal on one or more occasions		
					Transaminases consistently <2x upper limit normal		
3	**Virology (within last 12 months)**				HbsAg+ve		
					Anti-Hbs protective		
					HCV RNA +ve		
					Anti-HIV+ve		
10	**Glucose tolerance test (within last 12 months)**				Normal		
					Impaired glucose tolerance		
					Diabetes		
12	**Calcium levels (over last 12 months)**				Normocalcaemic on treatment		
					Normocalcaemic not on treatment		
					Hypocalcaemia on one or more occasions		
12	**Thyroid function tests (over last 12 months)**				Euthyroid off treatment		
					Euthyroid on treatment		
					Hypothyroid on one or more occasions		
10	**Cardiac review (within last 12 months)**				Normal		
					Cardiac arrythmia		
					Cardiac failure		
10	**Endocrine review (within last 12 months)**				Growth Hormone deficient		
					Normal puberty		
					Delayed puberty*		
					Hypogonadism (see definitions, section B1.5)		

10	**Audiometry (within last 12 months)**				Normal		
					Hearing loss		
10	**Ophthalmology (within last 12 months)**				Normal		
					Abnormal		
10	**Liver iron (within last 12 months, biopsy or MRI estimation)**				<7mg/g dry wt		
					7-15mg/g dry wt		
					>15mg/g dry wt		
10	**Cardiac T2* MRI (within last 12 months)**				T2*>20ms		
					T2* 10-20 ms		
					T2*<10 ms		
10	**DEXA bone scan (within last 18 - 24 months)**				Normal		
					Osteopenia (spine S, hip H, or both B)		
					Osteoporosis (spine S, hip H, or both B)		
					On treatment? Indicate what Rx		

Key Clinical Events

Date	Event	Yes/No	Comment / detail.
	Yersinia		
	Other Sepsis		
	Fracture		
	Heart failure		
	Dysrrythmia		
	Splenectomy		
	Cholecystectomy		
	Other operation		
	Bone marrow transplantation		
	Death		
	Other		

Vaccinations given:

Hepatitis B vaccine	Date last given:	Hep BsAb level * (date) :
Pneumococcal vaccine (if spleen out)	Date last given:	
HiB vaccine "	Date given:	
Meningococcal vaccine "	Date given:	

B

Summary guide to routine investigations and management

It will be a matter for local discussion which of the monitoring tests is undertaken at the local Clinic in advance of, or at the Centre during, the Annual Review visit. Communication of results between Clinic and Centre will be key to the effectiveness of these visits.

Where test results become abnormal between annual reviews, clinics are encouraged to discuss results with the Centre to decide on need to refer/start additional treatment.

For initial investigations on the newly diagnosed infant or child, please refer to Sections 5 and 6.

B.1 Growth and development

B1.1 Record parental heights at first visit

B1.2 Height (standing and sitting) and weight at least 6 monthly, plotted on appropriate growth and velocity charts

B1.3 Puberty staging, yearly from 10 years

B1.4 Enquire regularly about onset of menstruation in girls, and thereafter ask intermittently to check that periods are continuing spontaneously

B1.5 If growth velocity falling, or no pubertal development by 13 in girls, 14 in boys, or arrested puberty, refer to paediatric Endocrinologist at Centre

B1.6 Any hormone replacement therapy recommended by the Endocrinologist should usually commence by age 16 years.

B.2 Iron levels

B2.1 Ferritin 3-monthly

B2.2 MRI-based quantitation of heart and liver iron, yearly or more frequently if levels are high and patient is receiving intensfied chelation.

B.3 Liver function

B3.1 Liver function tests 3-monthly

B3.2 Ultrasound for gallstones if obstructive picture

B3.3 Viral hepatitis – see below

B.4 Cardiac function

B4.1 Clinical examination of the cardiovascular system at least 6 monthly

B4.2 Specialist cardiac function assessment annually from age 10

B4.3 Urgent referral to Centre Cardiologist if any suspicion of cardiac symptoms of signs between regular assessments.

B.5 Endocrine function

B5.1 Glucose metabolism

B5.1.1 Random blood glucose every 3-6 months and oral glucose tolerance test if elevated

B5.1.2 Oral GTT routinely annually from puberty - or from 10 years if positive family history

B5.1.3 Dietetic input for impaired glucose tolerance

B5.1.4 Diabetes team review if indicated

B5.2 Thyroid

B5.2.1 Annual TFTs - T4/FreeT4 and TSH from 12 or on clinical suspicion

B5.2.2 Refer to paediatric Endocrinologist and thyroxine replacement if indicated

B5.2.3 Check response to treatment and adjust dose if required 3 monthly initially or as advised by local specialist

B5.3 Parathyroid

B5.3.1 3-6 monthly calcium and phosphate measurements from age 12

B5.3.2 Measure Parathyroid Hormone if calcium low

B5.3.3 Treatment with oral vitamin D or analogue and calcium, usually in conjunction with Endocrinologist

B5.3.4 Monitor efficacy of treatment with calcium and phosphate levels 3 monthly

B.6 Chelator toxicity

B6.1 Audiometry yearly from 10 years if receiving desferrioxamine.

B6.2 Ophthalmology yearly from 10 years if receiving desferrioxamine.

B6.3 Frequent full blood count if receiving deferiprone.

B6.4 Assess zinc levels every three months and supplement if low.

B.7 Osteopenia/osteoporosis

B7.1 Advice re calcium-rich diet, importance of exercise, avoid smoking

B7.2 Bone densitometry (DEXA scanning) every 18 – 24 months, or annually if there is concern, from age 10 years

B7.3 Replacement of any hormone deficiencies

B7.4 For patients over the age of 16 consider treatment with bisphosphonates if osteopenic or osteoporotic

B.8 Viral screening

B8.1 Hepatitis C serology annually

B8.2 Hepatitis B surface antibody titre, at intervals recommended by local virology laboratory on the basis of existing antibody titre

B8.3 Boost hepatitis B vaccination when hepatitis B surface antibody level falls to level advised by microbiology lab

B8.4 HIV testing, with pre-test counselling, if transfused abroad, or if requested by patient or family, or if clinical concerns

B.9 Consideration of splenectomy and infection prophylaxis after splenectomy

B9.1 Review of red cell use and splenic size to consider splenectomy

B9.2 If splenectomy planned, pneumococcal immunisation and check HiB and meningococcal vaccine have been given

B9.3 Advise and repeat prescribe penicillin prophylaxis

B9.4 Offer travel precautions as for other splenectomised patients

B9.5 Issue 'splenectomy card' if locally used

B9.6 Consider aspirin 75 mg daily for persistent thrombocytosis after splenectomy [>750 x 10^9/l], although aspirin is avoided in children (<16 years).

B.10 Referral for consideration of Bone Marrow Transplantation

B10.1 All families who have a child with transfusion dependent beta thalassaemia major should be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, regardless of there being an available donor at the time.

C

Performance Indicators

C.1 Monitoring Services - delivery and effectiveness tool for audit of local services against standards

Monitoring of equitable access to, and effective delivery of, healthcare can be undertaken by use of the following Quality Standards, developed from the recommendations in the 2005 Edition of this document, and from 'Sickle Cell Disease in Childhood; standards and guidelines for clinical care' 2006. These are included here [with thanks to Jane Eminson, who authored them] . They will form the basis of a systematic peer review programme, starting to visit Centres / Networks in the near future.

Quality Requirements for Health Services Caring for Children and Young People with Haemoglobinopathies

Version 1

August 2007

Review by: December 2012

Introduction

These Quality Requirements have been developed to support implementation within services for children and young people of the *'Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK'* and *'Sickle Cell Diseases in Childhood: Standards and Guidelines for Clinical Care'*[1]. They reflect the aims, standards and guidelines of both documents. They also support the principles of the National Service Framework for Children, Young People and Maternity Services[2]. The Quality Requirements do not cover the national screening programme and its immediate follow up procedures. The Quality Requirements apply only to the care of children and young people and therefore do not cover the aspects of the *'Standards and guidelines for clinical care'* which relate to adult patients only. At a later stage, the Quality Requirements may be extended to cover the care of adult patients.

Standards and guidance can be interpreted in different ways and may not always be implemented in full. These Quality Requirements clarify the arrangements that should be in place and provide the answer to the question: "For each service, how will I know that the '*Standards and Guidelines for Clinical Care'* have been implemented?" The Quality Requirements are suitable for use in self-assessment or peer review visits.

As with the Standards documents, these Quality Requirements describe what services should be aiming to provide. All services should be working towards meeting all applicable Quality Requirements within the next two to five years.

Development of the Quality Requirements took place during 2006 and early 2007 through a sub-group of the UK Forum on Haemoglobinopathy Disorders. The suitability of the Quality

1. *Sickle Cell Diseases in Childhood - Standard and Guidelines for Clinical Care* (2006) is available on the publications section of the NHS Screening website: www.sickleandthal.org.uk . *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK* (2005) is available in the downloads section of the UK Thalassaemia website: www.ukts.org
2. Department of Health, *National Service Framework for Children, Young People and Maternity Services.* 2004

Requirements for use in peer review was tested in a pilot visit to the Royal London Hospital in January 2007.

Structure of the Quality Requirements

Topics: The Quality Requirements (QRs) are divided into the following topics:

- Specialist and Local Haemoglobinopathy Teams (SHT / LHT)
- Commissioners of services

More detail of the functions of each type of service is given in the *Standards for the Clinical Care of Children and Adults with Beta Haemoglobinopathy in the UK'* and *'Sickle Cell Diseases in Childhood: Standards and Guidelines for Clinical Care'*.

Some services will treat mainly children and young people with either sickle cell disease or thalassaemia and some Quality Requirements – or parts of Quality Requirements – are therefore applicable only to sickle cell disease only (SC) or thalassaemia only (T). Some teams will care for patients with all types of haemoglobinopathy and will be expected to meet both 'SC' and 'T' Quality Requirements. Quality Requirements relating to the care of patients with thalassaemia are also applicable to teams treating children and young people with sickle cell disease who need regular transfusion.

Specialist Haemoglobinopathy Teams may also provide local care for some patients.

Responsibilities

- Commissioners of services are responsible for achieving QRs 52 and 53 – with advice from providers of services for children and young people with haemoglobinopathies.
- Responsibility for achieving QRs 7 to 19 is shared between commissioners and providers of services (in particular, senior management within provider Trusts).
- QRs 1 to 6 and 20 to 51 are the responsibility of the nominated lead consultants and nurses (QRs 7, 9, 11 and 12), working in cooperation.

Sections: Each Quality Requirement has the following sections:

Reference number	This number is unique to these Quality Requirements and is used for all cross-referencing within the Quality Requirements. The section also indicates the type of team to which each Quality Requirement is applicable.
Quality requirement	This describes the standard that hospital Trusts and specialist commissioning arrangements are expected to meet.
Demonstration of Compliance	This describes how organisations may show that they are meeting the Quality Requirement. This is not prescriptive. Organisations may have other ways of showing that they meet the requirement.
Notes	The notes give more detail about either the interpretation or the applicability of the Quality Requirement.

Abbreviations:

LHT Local Haemoglobinopathy Team

SHT Specialist Haemoglobinopathy Team

SC Sickle cell disease

T Thalassaemia

Specialist and Local Haemoglobinopathy Teams

Information And Support For Patients and Their Carers

Ref	Quality Requirement	Demonstration of Compliance
1 LHT SHT	Written information should be offered to patients and their families covering at least: 1 A simple explanation and description of the condition, how it might affect the individual, possible complications and treatment. For sickle cell disease this information should include: a Problems, symptoms and signs for which emergency advice should be sought b How to manage pain at home, including how to avoid pain and non-pharmacological interventions c Importance of adequate fluid intake d Use of antipyretics for fever e Importance of regular antibiotics and full immunisation f How to feel the spleen and its significance. For thalassaemia this information should include: a Problems, symptoms and signs for which emergency advice should be sought b The importance of maintaining good haemoglobin levels by transfusion c Potential problems of iron load and how it can be managed. 2 Details of the services available locally including: a Clinic times and how to change an appointment b Key contact name and number c Alternative contact if key contact away d Who to contact for advice out of hours e How to use emergency services f Ward usually admitted to and its visiting times g Community services and their contact numbers h Details of support groups available. 3 Health promotional material including a Inheritance and implications for other family members b The importance of a good diet and regular exercise c Implications for travel d Age appropriate information on avoiding smoking and excess alcohol consumption e Age appropriate information on contraception and sexual health f Where to go for further information, including useful websites and national voluntary organisations.	Examples of written information available Notes: 1 Information may be from a recognised, published resource such as 'Sickle cell disease – a guide for parents' / 'What is thalassaemia', or a local document. 2 Information available should relate to the disease type/s treated by the team. 3 Information should be available in formats and languages appropriate to the needs of the patients. This may include large print and taped information. 4 Age-appropriate information as well as information for parents should be available. 5 Information may be given at different stages in the patient's care, as appropriate.
2 LHT SHT	Written information for the patient's primary health care team should be available covering at least: a All aspects of QR1 b The need for regular prescriptions, penicillin and analgesia (SC)	Examples of written information for primary health care teams Note: The information on regular prescriptions, penicillin and analgesia may be in the form of a clinic letter or additional information.
3 LHT SHT	Information should be available on transition to adult care. This information should cover all aspects of the transition (QR43).	Examples of age-appropriate information for young people and information for parents.
4 SHT	The SHT and its linked LHTs should have agreed a patient-held record for recording at least: a Information about the patient's condition b Current management plan c Regular medication d Named contact for queries and advice e Alternative contact for times when key contact is away.	Example of patient-held record. Note: Although responsibility for achieving this QR is given to the SHT, LHTs should cooperate with the SHT in the development and agreement of the patient-held record.
5 LHT SHT	The locally agreed patient-held record (QR4) should be in regular use within the LHT / SHT.	Discussion with staff and patients. Examples of completed records.
6 LHT SHT	Services should be provided in a child friendly environment, including toys and books / magazines for children and young people of all ages.	Facilities available

Staffing And Support Services

7 LHT	The LHT should have a nominated lead paediatrician / paediatric haematologist with responsibility for guidelines, protocols, training, audit relating to haemoglobinopathies, liaison with community services and overall responsibility for liaison with the SHT. The lead consultant should undertake CME activity of relevance to care of children and young people with haemoglobinopathies.	Name of lead paediatrician / paediatric haematologist. Note: The lead paediatrician may be community or hospital-based.

8 LHT	There should be agreed arrangements for cover for absences of the lead paediatrician.	Details of cover arrangements Note: Cover arrangements may be a second paediatrician within the LHT OR may be guidelines, agreed with the SHT, for contacting the SHT for advice.
9 SHT	The SHT should have a nominated lead paediatrician / paediatric haematologist consultant with an interest in the care of patients with haemoglobinopathies who should have responsibility for guidelines, protocols, training, audit relating to haemoglobinopathies and overall responsibility for liaison with referring LHTs. The lead consultant should undertake CME activity of relevance to care of children and young people with haemoglobinopathies.	Name of lead consultant. Note: The lead consultant may also have responsibility for liaison with community services for patients for whom local care is provided.
10 SHT	The lead consultant (QR9) should have a named deputy who will provide cover for absences. The named deputy in the SHT should undertake CME activity of relevance to care of children and young people with haemoglobinopathies.	Name of deputy.
11 LHT	The LHT should have a lead nurse who has responsibility, with the lead consultant (QR7), for guidelines, protocols, training, audit relating to haemoglobinopathies, liaison with community services and liaison with the SHT. The lead nurse should have specific training in the care of patients with haemoglobinopathies.	Name of lead nurse and details of relevant training. Note: The lead nurse may be community or hospital-based.
12 SHT	The SHT should have a lead haemoglobinopathy nurse with responsibility, with the lead consultant (QR9), for guidelines, protocols, training, audit relating to haemoglobinopathies and liaison with referring LHTs. The lead nurse should have specific training in the care of patients with haemoglobinopathies.	Name of lead nurse and details of relevant training. Note: The lead nurse may also have responsibility for liaison with community services for patients for whom local care is provided.
13 SHT	The SHT should have a nurse specialist or counsellor who provides outreach support for patients in the community. This nurse specialist / counsellor should have specific training in the care of patients with haemoglobinopathies.	Name of nurse specialist or counsellor and details of relevant training.
14 SHT	There should be agreed cover arrangements for the outreach nurse specialist / counsellor.	Details of cover arrangements
15 SHT	Access to the following staff and services should be available: a MRI and CT scanning b Transcranial Doppler ultrasonography (SC) c Hospital dental services d Genetics services e Bone marrow transplantation services f Contraception and sexual health services g Consultant cardiologist h Consultant endocrinologist i Consultant hepatologist j Consultant neurologist k Consultant ophthalmologist l Consultant orthopaedic surgeon m Consultant obstetrician n Child and adolescent mental health services	Details of services available Notes: 1 SHTs should ensure access to an appropriate level of specialist expertise in the care of patients with haemoglobinopathies. This may be through services within the same Trust or through cooperation with other Trusts or SHTs. It should be indicated where each service is available to children attending the unit, if not on site. 2 Some services may also be available within LHT facilities.
16 SHT	The following services should be available a Paediatric high dependency care b Paediatric intensive care There should be agreed criteria for admission to each level of care.	Details of services available. Criteria for admission. An audit of admissions to high dependency and intensive care is a desirable additional demonstration of compliance. Note: Where high dependency or intensive care services are located on a different hospital site to the haemoglobinopathy service, details of transfer arrangements should also be available.
17 SHT LHT	The following support services should be available: a Interpreters b Social work c Play specialist d Hospital teacher (in-patient care only) e Child psychologist f Dietician	Details of services available Note: These services may be hospital or community/ primary care based. They should be able to provide a timely response to the needs of patients with haemoglobinopathies.

18 SHT LHT	A service agreement for support from community services should be in place. This service agreement should cover, at least: a Guidelines for involvement of community paediatric services in the care of patients with haemoglobinopathies b Role of community services c Link worker within the hospital service d Exchange of information between hospital and community services and vice versa e Arrangements for liaison with schools.	Service agreement with relevant community services. Note: Where community and hospital services are managed by the same Trust an agreement cover these issues is still required.
19 SHT LHT	A nurse with competency in cannulation, starting and supervising a transfusion should be available at all times at which children are attending for transfusion.	Details of staff availability Evidence of competences of nursing staff. Note: Each service should have a method of regularly assuring the competence of nursing staff in cannulation, starting and supervising transfusions. This may be through external training or in-house assurance of competence. Details of the system used, the frequency of updating, the nurses who have reached this level of competence and staffing rotas will be needed to demonstrate compliance with this standard.
20 SHT LHT	All staff involved in the care of children and young people with haemoglobinopathies should undertake regular child protection training.	Details of training undertaken for core members of LHT / SHT.

Clinical And Referral Guidelines

NB. All clinical and referral guidelines should be based on the 'Standards for the Clinical Care of Children and Adults with Beta Thalassaemia in the UK' and 'Sickle Cell Diseasse in Childhood: Standards and Guidelines for Clinical Care.'

21 SHT	Guidelines should be in use covering a How to establish and confirm diagnosis b Parent and sibling testing	Clinical guidelines
22 SHT LHT	Clinical guidelines should be in use covering: a Recommended immunisations b Immunisations, other prophylaxis and travel advice prior to travel abroad. c Penicillin prophylaxis while awaiting clarification of diagnosis (SC only)	Clinical guidelines Note: The LHT clinical guidelines should have been agreed with the SHT to which patients are usually referred.
23 LHT SHT	Clinical guidelines should be in use covering possible acute presentations including: For patients with sickle cell disease: a Fever and infection including major sepsis b Acute pain c Acute anaemia d Stroke and other acute ischaemic events e Acute chest syndrome f Acute splenic sequestration g Abdominal pain and jaundice h Priapism i Changes in vision, including urgent referral for an ophthalmologic opinion j Cardiac problems k Endocrine problems l Indications for exchange transfusion m Practical protocol for exchange transfusion. For patients with thalassaemia: a Fever and infection including major sepsis b Unexpected cardiac, hepatic, endocrine decompensation. These guidelines should ensure that patients are transferred to the paediatric ward for assessment as quickly as possible	Clinical guidelines Note: Teams treating only patients with sickle cell disease or only patients with thalassaemia need guidelines relating to that group of patients.

24 LHT SHT	Clinical guidelines should be in use covering routine out-patient monitoring and management between formal annual progress review visits, including: All patients: a General assessment of well-being including school attendance b Any difficulties adhering to treatment or other difficulties with care c Monitoring growth and development d Checking for palpable spleen and demonstrating to parents / carers how to check for enlargement Patients with sickle cell disease: e Check history of priapism f Monitoring of oxygen saturation g Management of nocturnal enuresis h Monitoring of Hb levels, renal function tests, liver function tests i Checking all necessary immunisations up to date j Penicillin therapy and alternative therapy for children who are allergic to penicillin k Discussion to ensure analgesics available for home use understood and effective l Assessment of cognitive function, learning and behavioural difficulties m Indications for early referral to specialist haemoglobinopathy team (LHT only) Patients with thalassaemia: a Monitoring Hb levels, liver function and other biochemistry b Indications for early referral to specialist haemoglobinopathy team (LHT only)	Clinical guidelines
25 SHT	Clinical guidelines should be in use covering **annual specialist review** visits including, at least: All patients: a Regularity of school attendance and reasons for absence b Any difficulties adhering to treatment or other difficulties with care c Monitoring growth and development, including review of centile charts d Health promotion and healthy lifestyle advice and support e Contraception and sexual health in relevant age group f Travel advice g Review Hb levels, renal and liver assessment, other biochemistry h Hepatitis B vaccination i Monitoring of hepatitis B antibodies and action to be taken should levels fall j Monitoring for hepatitis C in transfused patients k Discussion and preparation of child for any planned surgery l Indications for consideration of splenectomy m Preparations for splenectomy including recommended immunisations n Treatment of complications of splenectomy, including persistent thrombocytosis. Patients with sickle cell disease: a As QR 24 plus b Monitoring and screening for neurological complications, including transcranial Doppler ultrasonography c Indications for imaging to assess the extent of cerebrovascular disease d Indications for overnight oxygen saturation monitoring (sleep study) e Indications for echocardiography including possibility of pulmonary hypertension Patients with thalassaemia: a As QRs 31 and 32 plus b Review annual red cell consumption c Review adequacy and appropriateness of iron chelation regimen d Consideration of options for helping children, young people and their families to adhere to chelation therapy e Audiometry and ophthalmology check for those on desferrioxamine, from age 10 f Cardiological assessment (from age 10) g Testing for endocrine abnormalities (from age 10) h Bone mineral density assessment (from age 10).	Review protocol Notes: 1 This QR is linked to QRs 28 and 29 2 The guidelines should be clear about the arrangements for multi-disciplinary review and involvement of members of the LHT / SHT. 3 The guidelines should ensure that the care of all patients is reviewed at least annually. 4 According to local network agreements, some aspects of care review can take place at the LHT and be communicated to SHT in time for the annual review visit 5 Other aspects, not covered by LHT, should be covered by SHT at review visit.

26 LHT SHT	Guidelines should be in use for referral of patients and their families to a clinical psychologist with experience in the care of patients with haemoglobinopathies (including the option for self-referral)	Clinical guidelines Notes: 1 As QR17. *2 These guidelines link to the review protocols (QRs 24 and 25)*
27 LHT SHT	Guidelines for referral for consideration of bone marrow transplantation should be in use.	Clinical guidelines

Quality Requirements 28 To 33 Apply Only To Teams Caring For Patients With Thalassaemia And / Or Patients With Sickle Cell Disease Who Need Regular Transfusions.

28 LHT SHT	Clinical guidelines should be in use covering: a Indications for regular transfusions b Investigations and vaccinations prior to first transfusion c Monitoring of haemoglobin levels	Clinical guidelines
29 LHT SHT	Clinical guidelines should be in use covering review by a specialist nurse or doctor prior to transfusion to ensure that each transfusion is appropriate.	Clinical guidelines
30 LHT SHT	A Transfusion Policy should be in use covering: a Area/s where transfusions will usually be given b Procedures for checking blood c Staff allowed to undertake cannulation d Recommended number of cannulation attempts e Maximum rate and volume of transfusion according to size of child f Monitoring the transfusions g Management of transfusion reactions h Arrangements for medical cover during transfusion i Arrangements for ensuring that a nurse with appropriate competences (QR19) is in attendance throughout the transfusion.	Transfusion Policy Notes: 1 Only medical staff and nurses with appropriate competences (QR19) should be allowed to undertake cannulation. 2 Both Standards documents recommend that no more than three cannulation attempts should be made on one individual. 3 Blood transfusions should be monitored and reactions managed according to the latest British Committee for Standards in Haematology guidelines. 4 The policy should ensure that patients do not usually wait for more than one hour for cannulation and setting up of the blood transfusion.
31 LHT SHT	Clinical guidelines for chelation therapy and monitoring iron load should be in use including: a Indications b Choice of regime c Dosage and dosage adjustment d Clinical assessment of tissue damage e Monitoring of serum ferritin f Use of non-invasive estimation of organ-specific iron loading heart and liver by T2*/R2 g Management of side effects of chelators.	Clinical guidelines Notes: 1 Initiation of combined chelation therapy should not be undertaken by the LHT without discussion with the clinical team at the SHT. 2 Dosage adjustment and management of complications should be discussed with the SHT prior to modification of the patient's management plan by the LHT. 3 The LHT clinical guidelines should have been agreed with the SHT to which patients are usually referred. 4 Guidelines should encourage patient and family involvement in monitoring wherever possible.
32 LHT SHT	Clinical guidelines for the management of thalassaemia intermedia should be in use including: a Indications for transfusion b Monitoring iron loading c Use of HbF promoters d Indications for splenectomy.	Clinical guidelines Notes: 1 This QR may be met by covering specific management issues around thalassaemia intermedia within QR28. 2 This QR is not applicable to teams treating only patients with sickle cell disease.
33 LHT SHT	Clinical guidelines should be in use covering: a Indications for exchange transfusion b Arrangements for carrying out an exchange transfusion.	Clinical guidelines

Service Organisation and Liaison With Other Services

34 LHT SHT	Clinical guidelines for acute and out-patient monitoring and management (QR23and QR24) should be available and in use in appropriate areas including A&E, clinic and ward areas.	Guidelines available in appropriate clinical areas. Note: Guidelines may be available in paper and / or electronic forms.

35 LHT SHT	A protocol should be in use covering the initial clinic visit for patients with haemoglobinopathies covering, at least: a Giving each patient information relevant to their condition (QR1) b Giving each patient their patient-held record (QR4) c Allocation of a named contact for queries and advice to each patient. d Discussion of arrangements for future treatment and care e Measurement of parents' height f Sending the GP information relevant to their patient's condition (QR2)	Written protocol Notes: 1 Arrangements for future treatment of care should include discussion of care at a LHT closer to the patient's home. 2 For children, the discussion will involve the parents as well as the child. 3 This QR is linked with QR39.
36 LHT SHT	A protocol should be in use covering the initial clinic visit for patients previously treated outside the UK, including: a Full medical history and examination b Investigations c Referral to other specialist services (QR15) d All aspects of QR28	Written protocol
37 SHT	A protocol should be in use covering arrangements for care between SHT and LHT for ongoing care. This protocol should ensure that, to facilitate effective shared care: a All patients have an up to date patient held record and details of their care plan. b The LHT and the patient's GP have received details of the patient's care plan.	Written protocol Note: The patient's care plan may be part of the patient-held record, be covered in clinic letters or can be a separate document.
38 LHT SHT	A protocol should be in use covering: a Updating patient-held records b Offering patients a permanent record of consultations at which changes to their care plan are discussed. c Changes of key contact d Giving further information (QR1) as patients' and families' needs change	Written protocol Notes: 1 The permanent record of consultations at which changes to care plans are discussed may be achieved through updating the patient-held record or may involve additional communication. 2 This QR relates to the LHT / SHT's internal arrangements. It should be consistent with the policy for communication between teams (QR39).
39 SHT	The SHT and its linked LHTs should have agreed a policy on the communication of clinical information, management plans and important decisions regarding treatment between clinical teams. This protocol should cover information from specialist clinic visits as well as contacts with SHT / LHTs. The protocol should be specific about frequency / indications for communication with the patient's GP	Policy agreed with referring LHTs. Note: Both Standards documents recommend that communication to the GP should be at least every 6 months and when there are new problems or treatment changes.
40 LHT SHT	An operational policy should be in use covering: a Teaching children, young people and their patients how to set up an administer subcutaneous desferrioxamine infusions b Encouraging children to participate in setting up and administering their own infusion c Regular assessment and updating administration techniques d Recording of assessments of administration techniques NB. This QR applies only to teams treating patients with thalassaemia and / or patients with sickle cell disease who require regular transfusion.	Operational policy Note: This policy should specify involvement of play specialists, hospital teaching staff, social workers, and clinical psychology in encouraging involvement in setting up and administration of chelation therapy and improving adherence to therapy.
41 LHT SHT	Patients and families should have choice of attending for blood tests, clinic appointments and blood transfusions 'out of hours' to minimise disruption to normal life	Details of arrangements
42 LHT SHT	A protocol should be in use covering: a Follow up of children who do not attend b Communication and follow up of children who move to another area	Written protocol
43 SHT	A protocol should be in use covering transition to adult care. This should ensure: a Age guidelines for timing of the transfer. b Involvement of the young person in the decision about transfer. c Involvement of primary health care, social care and adult services in planning the transfer. d Allocation of a named coordinator for the transfer of care. e A preparation period and education programme relating to transfer to adult care. f Communication of clinical information to the adult services. g Arrangements for monitoring during the time immediately after transfer to adult care.	Protocol agreed with adult services to which patients are usually transferred. Note: The named coordinator may change during the young person's transition to adult care and will normally be the same as the young person's key contact (QR1).

44 LHT SHT	The team should have in place: a Mechanisms for receiving feedback from patients and carers about the treatment and care they receive. b Mechanisms for involving patients and carers in decisions about the organisation of the services. c Mechanisms for encouraging the development of local support groups.	Description of current arrangements. Examples of changes made as a result of feedback from patients and carers. Details of local support groups Note: The arrangements for receiving feedback from patients and carers may involve surveys, focus groups and/or other arrangements. They may be part of Trust-wide arrangements so long as issues relating to haemoglobinopathy services can be identified.
45 SHT	The SHT should run a programme of training and awareness of the management of patients with haemoglobinopathy for its main referring LHTs.	Details of training and awareness programme
46 LHT	Staff from the LHT should participate in the training and awareness programme run by the SHT to which patients are usually referred.	Details of participation in training and awareness programme.
47 SHT	The SHT should meet at least annually with its referring LHT teams to: a Identify any changes needed to network-wide policies, procedures and guidelines b Review results of audits undertaken c Review any critical incidents including those involving liaison between teams d Consider the content of future training and awareness programmes (QR45)	Evidence of review meeting/s having taken place. Note: Meetings may be with referring teams together or separately.
48 LHT	A representative of the LHT should attend each review meeting with the SHT to which patients are usually referred (QR47).	Evidence of attendance at meetings with main SHT.
49 SHT	The SHT should meet at least annually with representatives of the neonatal screening programme to review progress, identify issues of mutual concern and agree action.	Notes of liaison meetings.

Data Collection and Audit

50 LHT SHT	The LHT / SHT should have audited compliance with key standards including: Patients with sickle cell disease: a Proportion of patients taking regular penicillin b Proportion of patients fully immunised against pneumococcus c Proportion of patients who have had Transcranial Doppler ultrasonography undertaken within the last year d Proportion of patients who have had their annual multi-disciplinary review within the last year e Effectiveness of action to contact families who have not attended for follow up appointments. f Review of the care of any patients who have died. Patients with thalassaemia: a Proportion of patients on regular transfusion b Proportion of patients on chelation therapy c Proportion of patients who have had their annual multi-disciplinary review within the last year d Adequacy of recording of: Pre-transfusion Hb levels Regular monitoring of iron level Complications of iron overload Height / weight progression Spleen size Support for home chelation programme (QR40) e Effectiveness of action to contact families who have not attended for follow up appointments. f Review of the care of any patients who have died.	Results of audit undertaken Mortality review procedure
51 SHT	The SHT should be submitting data on all patients to the national haemoglobinopathy audit programme (when established).	Latest national haemoglobinopathy audit programme report showing data from SHT.

Commissioners of Services

2	Each Specialist Commissioning Group[a] should have agreed the location of services for its population: a Specialist Haemoglobinopathy Team/s for children and young people b Local Haemoglobinopathy Team/s for children and young people c The expected referral patterns to each SHT and LHT. d The type of patients (sickle cell and / or thalassaemia) who will be treated by each team.	Agreed configuration of services and expected referral patterns. Notes: 1 SHTs and LHTs may be located within or outside the area served by the SCG. 2 Individual children and young people may be referred to Teams other than those specified for clinical reasons, ease of access or patient choice.

3	Each Specialist Commissioning Group should have: a Compared the staffing, support services and facilities of each SHT and LHT located within its area (QR 52) with the levels expected in QRs 7 to 19. b Agreed a plan for the development of SHTs and LHTs located within its area. c Monitored achievement of the agreed plan at least annually. The agreed development plan should ensure that QRs 7 to 19 are met within 2 to 5 years.	Review of current services. Agreed strategic development plan Notes: 1 SHTs may take referrals from more than one Specialist Commissioning Group area. If so, the development plan should be agreed with the main referring Specialist Commissioning Groups. 2 This QR aims to ensure that each SHT and LHT has a development plan agreed with its main commissioners. This does not replace the individual discussions between commissioning organisations and service providers. All commissioners will be expected, however, to work within the agreed development plan.
Ref.	**Quality requirement (QR)**	**Demonstration of Compliance**

a. The structure of Specialist Commissioning Groups is currently subject to review. These Quality Requirements apply to whichever organisation has the responsibility for coordinated commissioning of services for patients with haemohinopathies.

C.2 Health Outcomes of Care

The following tables are intended for local clinics and Centres to audit the progress of patients under their care.

	Number of patients
Paediatric (<16 years) thalassaemia patients managed (specify regularly transfused / not)	
+ Adult (16 years and over) thalassaemia patients managed (specify regularly transfused / not)	
= Total number of thalassaemia patients managed: (regularly transfused / not)	

Investigation/ measurement	Result	Total number of patients to whom applies	Number of new patients in-year to whom applies	Comments
Growth	Height progressing along satisfactory centile			
	Growth velocity unsatisfactory			
Physical examination	Bone changes			
	Splenomegaly			
	Hepatomegaly			
Average Hb (pre-transfusion)	<9.5 g/dl			
	9.5-10.5 g/dl			
	>10.5 g/dl			
Average serum Ferritin	<1000			
	1000-2500			
	>2500			
Liver function tests (over last 12 months)	Transaminase >2x upper limit of normal on one or more occasions			
	Transaminase consistently <2x upper limit normal			
Virology (within last 12 months)	HbsAg+ve			
	Anti-Hbs protective			
	HCV RNA +ve			
	Anti-HIV+ve			
Glucose tolerance test (within last 12 months)	Normal			
	Impaired glucose tolerance			
	Diabetes			
Calcium levels (over last 12 months)	Normocalcaemic on treatment			
	Normocalcaemic not on treatment			
	Hypocalcaemia on one or more occasions			
Thyroid function tests (over last 12 months)	Euthyroid off treatment			
	Euthyroid on treatment			
	Hypothyroid on one or more occasions			
Cardiac review (within last 12 months)	Normal			
	Cardiac arrythmia			
	Cardiac failure			
	T2* undetectable iron			
	T2* mild cardiac iron			
	T2* moderate cardiac iron			
	T2* severe cardiac iron			

Endocrine review (within last 12 months)	Growth Hormone deficient			
	Normal puberty			
	Delayed puberty*			
	Hypogonadism* (* see definitions, section B.15)			
	On treatment			
	Off treatment			
Audiometry (within last 12 months)	Normal			
	Hearing loss			
Ophthalmology (within last 12 months)	Normal			
	Abnormal			
Liver iron (within last 12 months, biopsy or MRI estimation)	<7mg/g dry wt			
	7-15mg/g dry wt			
	>15mg/g dry wt			
DEXA bone scan (within last 18 - 24 months)	Normal			
	Osteopenia (indicate if at spine or hip, or both)			
	Osteoporosis (indicate if at spine or hip, or both)			
	On bisphosphonate treatment			

Key Clinical Events

Event	Number of patients	Comment / detail
Significant infection: specify organisms (e.g. Yersinia, Klebsiella, etc.)		
Fracture		
Heart failure		
Dysrythmia		
Splenectomy		
Cholecystectomy		
Other operation		
Bone marrow transplantation		
Death		
Other		

D

Levels of Evidence

D.1 Grading of Recommendations

Grade Type of recommendation (based on AHCPR 1992)

A (levels I a, I b)

Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation

B (levels I a, I b, III)

Requires availability of well conducted clinical studies but no randomized clinical trials on the topic of the recommendation

C (Level IV)

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable formal studies.

E

Glossary

adherence
the extent to which a person is able to take medication exactly as prescribed.

aetiology
cause.

agranulocytosis
absence or very low levels of granulocytes (neutrophils), the white blood cells which fight off bacterial and fungal infections.

alpha fetoprotein
a chemical marker which can be measured in the blood. Its level is raised in, for example, liver cancer and in some circumstances during pregnancy.

alpha globin
one of the two proteins required to make adult type haemoglobin, the other being beta globin.

amenorrhoea
absence of menstrual periods

anaemia
low blood level, specifically low level of haemoglobin (the red oxygen carrying pigment inside the red blood cells).

anomaly
abnormality, usually of development

antenatal
literally "before birth", meaning during pregnancy.

antibiotic
medication to treat bacterial infections

antibody
protein the body's immune system makes in response to infection, to fight it off. Antibodies can be artificially provoked by immunisation/vaccination to try to prevent infection. Additionally, antibodies can form against other 'unfamiliar' proteins, for example after blood transfusion, against some of the proteins on the surface of the transfused red cells.

appendix/appendicitis/appendicectomy
small elongated projection at the beginning of the large bowel, which has no useful function in humans. It can become inflamed causing pain and fever (appendicitis) and may need to be removed (appendicectomy).

arthritis
painful inflammation and swelling in joints.

arthropathy
pain in the joints.

audiology
clinical speciality of managing hearing.

audiometry
measurement of hearing.

autosomal recessive
a gene which can be passed on to offspring by a mother or a father, and which if inherited with a "normal" equivalent gene from the other parent, gives rise to no health problems (a healthy carrier). In order to develop a clinical condition, it needs to be inherited from both parents.

bacteraemia
infection in which bacterial organisms circulate in the blood.

bart's hydrops fetalis
an unusual condition, which usually causes a late miscarriage or stillborn baby, caused by the foetus inheriting no functioning alpha globin genes from either parent. Alpha globin is one of the two proteins required to make adult type haemoglobin, the other being beta globin.

beta globin
one of the two proteins required to make adult type haemoglobin, the other being alpha globin.

biliary tract
the tube system leading from the liver into the small bowel, and carrying bile. This has the dual purpose of aiding digestion and carrying waste products such as bilirubin formed when haemoglobin is broken down in the liver. The gall bladder is a small storage pouch for bile between the liver and bowel.

biopsy
a small sample of tissue removed for microscopic or other examination, in order to aid diagnosis or guide treatment.

bisphosphonates
a group of drugs which help put calcium back into the bones.

bone marrow transplant
a major medical procedure in which the patient's bone marrow, usually because of a condition such as thalassaemia or leukaemia, is replaced by bone marrow from a healthy donor of the same or very closely matched tissue type.

bone resorption
a normal process in which bones are being continually eaten away at their surface. It goes along with new bone formation, and the result of the two is called bone remodelling

butyrate
a naturally occurring fatty acid chemical which has been shown to increase production of foetal or baby type haemoglobin in certain circumstances.

carcinoma
the most common type of cancer or tumour.

cardiac arrhythmia
disturbance of the normal, regular heart rhythm.

cardiac decompensation
failure of the heart's pumping mechanism to work strongly enough.

cardiologist
doctor specialising in cardiology.

cardiology
clinical speciality of managing heart disorders.

cardiomyopathy
problem in the heart muscle, weakening the pumping action.

cartilaginous dysplasia
abnormality of the developing cartilage, the smooth material at bone ends causing joints to move smoothly.

chelation
removal of excess iron from the body, using a specific medication called a chelator.

chimerism/mixed chimerism
a situation following bone marrow transplant in which the patient's own bone marrow remains functional alongside the donor bone marrow.

chlamydia
a micro-organism sometimes found in the cervix, which can cause fertility problems(?)

cholecystitis
inflammation of the gall bladder.

cholecystectomy
surgical removal of the gall bladder.

cholelithiasis
stones in the gall bladder or biliary tract.

chorionic villus sampling
procedure, usually undertaken at 11 or 12 weeks of pregnancy, to remove a small piece of the placenta in order to test for a condition which may affect the fetus.

cirrhosis
a liver disease which can be caused by a range of problems, in which the liver is scarred with areas of functioning liver tissue trapped between scar tissue bands

colic
spasms of pain caused when a hollow organ is blocked, for example, the bowel or tubes of the biliary tract

ct scan
computerised tomography imaging technique which interprets multiple X-ray images to visualise internal anatomy

cystic fibrosis
an autosomal recessive condition, in which the affected individual has chronic cough, repeated lung infections and difficulty with digestion

deferasirox
an iron chelating drug which is active when taken by mouth. Its original name was ICL670 and it is licensed under the name Exjade.

deferiprone
an iron chelating drug which is active when taken by mouth. Its original name was L1, and it is licensed under the name Ferriprox.

densitrometry (bone)
measurement of bone density or strength of the bones.

desferrioxamine
the first available iron chelating medication which is still the most commonly used. It is licensed under the name Desferal. It is not active when taken by mouth.

diabetes mellitus
a condition in which the body is unable to process carbohydrates and sugars properly.

diabetes Type 2
a type of diabetes which is usually of later onset, and which frequently responds to diet or tablets rather than needing insulin.

diagnostic imaging
a general term for any sort of X-ray or scan used to aid diagnosis.

disc disease
problems affecting the soft tissue discs which sit between the spinal bones and aid spinal movement.

diuretic
a medication which increases the kidneys' output of salt and water, causing an increase in urine output.

dysrhythmia
disturbance in the heart's normal, regular rhythm.

echocardiography
an ultrasound scan of the heart in which the movement of the heart muscle and heart valves can be visualised.

electrophoresis
a laboratory technique in which different proteins in solution are separated, by passing a weak electric current through the solution.

endocrine
relating to hormones

endocrinologist
a medical specialist in conditions causing hormone disturbance

endocrinopathy
a condition affecting the hormone producing glands

enzyme
: a protein chemical which speeds up metabolic processes in the cells of the body. The level of certain enzymes can be measured and may give a guide to the condition of the organ producing them (for example, liver enzymes).

epiphyseal fusion
: epiphyses are the ends of the growing bones. When a person is reaching maturity, the epiphyses fuse or lock together with the main part of the bone in certain areas, after which no more growth can occur.

erythroid
: relating to red cell production

erythroid marrow hyperplasia
: overgrowth of the bone marrow caused by increased red cell production.

erythropoiesis
: the process of red cell formation.

erythropoietin
: the hormone produced by the kidneys which drives red cell production.

fallopian tube
: the tube which connects the ovary to the body of the uterus or womb.

ferritin
: a soluble transport form of iron, which can be measured in the blood and used as an indication of the total amount of iron in the body.

fetus (also spelt foetus)
: the unborn baby.

folic acid
: a vitamin of the B group which is required for red cell formation. It is found in green leafy vegetables and nuts.

fracture
: breakage (of a bone).

fulminant
: full-blown or obvious.

G6PD deficiency
: low levels of a chemical called glucose 6 phosphate dehydrogenase, found in the red cells, which is used by the red cells to resist damage by certain chemicals. Deficiency is an inherited condition, usually causing few problems but which can lead to red cell breakdown, especially if a person takes certain medications which should therefore be avoided.

gall bladder
: is a small storage pouch for bile, positioned on the biliary duct or tube between the liver and bowel

gall stone
: a lump of hard material developing in the biliary system or gall bladder

gene
: an inherited instruction which determines one or a number of functions which occur in the chemical machinery of the cell. The gene consists of a stretch of DNA containing unique coding sequence which is eventually translated into a protein. This sequence is copied as the cell divides

genetic
: relating to one or more genes

geneticist
: scientist or doctor who has a specialist interest in conditions caused by genetic problems

genotype
: a particular type or combination of genetic changes

genu valgum
: tendency to have "knock knees".

globin
: the protein parts of the haemoglobin molecule.

glucose intolerance
: a mild form of inability of the body to handle glucose and sugars optimally, not as severe as diabetes mellitus.

gonadal
: relating to the organs of reproduction; ovaries in women and testes in men.

graft rejection
: a situation where, after a transplant (for example, of bone marrow), the immune system of the person receiving the transplant reacts against it and tends to destroy it.

graft versus host disease/GVHD
: a condition following a transplant in which the functioning immune cells in the transplanted tissue react against and damage tissues of the person receiving the transplant.

gram negative/gram positive organism
: bacteria which either do (positive) or do not (negative) stain with a reagent called Gram's stain, used by laboratories to differentiate organisms viewed under the microscope.

growth hormone deficiency
: a shortage of a hormone produced by the pituitary gland which is chiefly responsible for controlling growth.

haematocrit
: percentage of the blood which is taken up by the blood cells as opposed to the fluid plasma.

haematology
: the clinical speciality relating to blood disorders.

haematologist
: medical specialist managing blood disorders.

haematopoiesis
: the process of blood cell formation, which usually takes place within the bone marrow. 'Extra-medullary haematopoiesis' describes the situation in which the tissue performing this function extends outside the bone margins

haemochromatosis
: a condition where the body gradually loads up with too much iron. The term usually refers to the hereditary sort, where too much iron is absorbed from the diet, rather than to the condition resulting from repeated blood transfusions.

haemoglobin
: the red, oxygen-carrying pigment which circulates in the red blood cells. From infancy onwards the majority type is adult-type or Haemoglobin A, and it is the beta globin protein part of this which cannot be made adequately in thalassaemia major.

haemoglobin H disease
: a condition resulting from inheritance of only one functioning alpha globin gene, of the usual four. It is usually quite a mild anaemia with not many clinical problems.

haemoglobinopathy
: a general term which covers all the inherited medical conditions which are due to abnormal or under-produced haemoglobin proteins.

haemolysis
: premature red cell breakdown

haemolytic
: resulting from premature red cell breakdown.

hepatic
: relating to the liver.

hepatitis
: inflammation of the liver.

hepatologist
: medical specialist in liver disorders.

hepatomegaly
: liver enlargement.

hepatosplenomegaly
liver and spleen enlargement.

heptaocellular carcinoma
cancer of the liver cells.

heterozygote
an individual who inherits one type of a gene from one parent, and another type from the other. Relating to haemoglobin disorders it most usually describes inheritance of a normal gene from one parent together with a thalassaemic or sickle gene from the other – the healthy carrier state.

high performance liquid chromatography (HPLC)
an automated, rapid and accurate way of separating different protein bands in a solution, for example, different sub-types of haemoglobin from a blood sample.

histology
the appearance of tissue examined under a microscope.

histopathology
the clinical speciality of analysing tissue specimens for abnormality.

HIV
the 'human immunodeficiency virus', which causes AIDS.

HLA/human leucocyte antigen
describes a set of proteins on the white blood cells. Commonly referred to as "tissue type".

homozygote
a person who inherits the same gene type from both parents, for example, beta thalassaemia major (beta thalassaemia gene from both parents) or haemoglobin SS sickle cell anaemia (sickle cell gene from both parents).

hormone replacement therapy
usually used to describe oestrogen hormones given to women after the menopause, but can also relate to the replacement of any hormone which is lacking because of underactivity of the endocrine glands.

HPFH (hereditary persistence of fetal haemoglobin)
continued production of fetal or baby type haemoglobin into adult life. This is an inherited feature.

hydroxyurea (also known as hydroxycarbomide)
a medication used for many years for bone marrow over-activity syndromes, but more recently found to be of use in sickle cell anaemia and to some extent in thalassaemia.

hyperglycaemia
elevated blood sugar.

hypersplenism
overactive spleen, often also enlarged, resulting in lowered blood counts.

hypertension
high blood pressure.

hypocalcaemia
low calcium level in the blood.

hypogonadism
failure of the normal activities of the testes in men, or ovaries in women.

hypogonadotrophic hypogonadism
hypogonadism resulting from underproduction of gonadotrophin hormones which are produced by a small gland inside the brain, and which normally drive ovarian/testicular function.

hypoparathyroidism
underactivity of the parathyroid glands which control body calcium levels.

hypothalamus
a small gland situated deep in the brain which, with the pituitary gland adjacent to it, controls many of the hormone producing glands.

hypothyroidism
underactivity of the thyroid gland, which controls the body's activity levels.

intermedia
when relating to thalassaemia, describes the condition in which, although a person inherits a thalassaemic gene from both parents, he/she can make enough haemoglobin to get along without always needing regular blood transfusions.

intrauterine
inside the uterus or womb.

laparoscopy
a procedure for looking and/or operating inside the abdomen through small, keyhole incisions.

laparotomy
an operation to open up the abdomen, using ordinary 'open' surgery

leukaemia
cancer of white blood cells.

malocclusion (dental)
the teeth do not meet properly when the jaws close.

meningitis
inflammation, usually by infection, of the meninges or brain coverings.

menopause
the time, in women, at which the ovaries stop producing eggs and the periods cease

metabolism
the body's chemical processes or activities.

monotherapy
single drug treatment.

morbidity
illness.

mortality
death.

MRI
magnetic resonance imaging, a scanning technique which gives clear pictures and no exposure to X-rays

MUGA
'multigated acquisition' scan, which uses injection of a radio-isotope to show up the heart muscle and measure its function

necrosis
tissue death

neonate
newborn.

nephropathy
kidney problem.

obstetrics
the medical speciality of caring for pregnant women and their unborn children, until after delivery.

oesophagus
the gullet connecting the mouth and stomach, down which the food is swallowed.

oesophagoscopy
a procedure to look down into the gullet.

ophthalmology
the clinical speciality of managing eye disease.

orthopaedics
the clinical speciality of managing bone and joint problems, particularly by surgery.

osteomalacia
bone weakness, usually resulting from lack of vitamin D or calcium.

osteopenia
a mild degree of bone thinning.

osteoporosis
: a more severe degree of bone thinning which can cause pain and increased risk of fracture.

ovary
: the organ in females which produces eggs.

ovulation
: egg production.

paediatrics
: the clinical speciality of caring for illness in children.

pamidronate
: a medication (one of the bisphosphonates) which can help put calcium back into bones).

parathyroid
: the glands which control calcium levels in the blood and bones, by producing parathyroid hormone.

pathogenic
: causing illness.

pathology
: the study of disease processes, and of diseased tissues or organs

pericarditis
: inflammation of the fibrous sac which surrounds the heart.

perinatal
: around the time of birth.

peri-operative
: around the time of an operation.

perioral
: around the mouth.

peripheral
: towards the edges, in medicine usually used to describe towards the hands and feet.

phenotype
: describes the structure or appearances resulting from different gene makeup, or **genotype**.

phlebotomy
: blood removal.

physiology
: the study of normal body processes.

physiotherapy
: the speciality of trying to improve joint and muscle function and mobility, often by massage, exercise etc.

pituitary
: a small gland deep inside the brain, which, with the hypothalamus which lies next to it, controls most of the body's hormone producing glands.

pneumococcus
: a type of bacteria (also known as **streptococcus pneumoniae)** which in most people causes tonsillitis, but in people whose spleen is absent or not working can get into the bloodstream and cause very serious infections.

polymorphism
: (literally "many forms") usually describing the possibility of different forms which can occur at a single gene site.

prenatal diagnosis
: diagnosis on a baby before birth.

prognosis
: outlook or expected outcome.

prophylaxis
: treatment given to try to prevent a problem, rather than waiting until it develops and then treating it.

pulmonary
relating to the lungs.
R2/R2*
a magnetic property of tissues which increases with raised iron content
radiology
the clinical speciality of interpreting X-rays and other diagnostic images.
radiotherapy
the clinical speciality of giving treatment with radiation.
renal
relating to the kidneys.
retina
the membrane at the back of the eye which senses light and sends messages to the brain, where they are interpreted into vision.
retinopathy
disease or problem affecting the retina.
rheumatology
the clinical speciality of managing joint disease (with medicine, not surgery).
rickets
a condition which arises when the bones are softened by lack of vitamin D or calcium (**osteomalacia**), and which can cause deformity in developing bones
rubella
virus infection more commonly known as 'German measles'.
sensorineural
usually used to describe a form of deafness due to damage to the auditory or hearing nerves.
sepsis
infection, usually bacterial.
septicaemia
infection in the blood.
serum
the clear fluid remaining when blood has been allowed to clot and the clot removed.
serology
testing of serum.
sickle cell disorders
a group of inherited conditions in which altered structure of haemoglobin can give rise to anaemia, sudden severe pain 'crises' and a range of other health problems
sinuses
air spaces within the bones of the face
sinusitis
inflammation, usually caused by infection, in the sinuses
spermatogenesis
formation of sperm by the testes
spleen
large organ lying under the lower ribs on the left, which helps in fighting infection and removes old or damaged cells from the blood
splenectomy
removal of the spleen
splenomegaly
enlarged spleen
staphylococcus epidermidis
a type of bacterium which can infect tubes or 'lines' put through the skin into the veins so that medication can be administered through them
stem cells
the earliest, most primitive cells in the body which can mature into almost any of the tissues

sub-clinical
not apparent as not causing symptoms, or signs on examination
subcutaneous
under the skin
synergy/synergistic
working together
T2/T2*
a magnetic property of tissues which falls with increased iron content
tetany
muscle spasm caused by low calcium level in the blood
thromboprophylaxis
medication given to try to prevent blood clots forming in the blood vessels
thrombosis
blood clot forming in the blood vessels
thyroid
the gland which produces thyroxine hormone, which controls the body's activity levels
transaminases
liver enzymes
UKCCSG
United Kingdom Children's Cancer Study Group
ultrasound
a type of scan using high frequency sound waves
vaccination
injection to provoke an immune response to an infection, and therefore protect against it
varices
enlarged vein containing blood at higher pressure than usual
vascular
to do with the blood vessels (intravascular – inside a blood vessel)
ventricles
when relating to the heart, indicates the main pumping chambers
vertebra(e)
bone(s) in the back or spine
paravertebral
around the vertebral bones
vertebral dysplasia
abnormality in development of the vertebrae
yersinia (enterocolitica)
bacterial organism which can cause infection in the bowel, giving severe pain and fever. It infects particularly people who have high iron levels and are on iron chelation.