Feasibility and Utility of a Sickle Cell Disease Registry for Research and Patient Management

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by

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Abstract

This thesis aimed to evaluate the feasibility and utility of a sickle cell disease registry for clinical patient management and research. Five hospitals out of nine in the North West London health region participated in the registry, with 78 percent coverage of the sickle cell disease population. There was 80% case ascertainment in participating hospitals.

Aggregated anonymised demographic and diagnostic data was collected for all haemoglobinopathy patients. This provided the core dataset for quantifying prevalence of sickle cell and thalassaemia and mapping local hospital workloads and service requirements. Thirteen percent of HbSS adult patients were taking hydroxycarbamide.

The cohort of patients treated with hydroxycarbamide was evaluated. Sixty two of the 80 patients started on treatment were included. Follow-up was censored after 9 years, totalling 249 person-years of data with a median follow-up of three years (IQR, 1-6). Results showed that haematological benefits were maintained in the long-term with treatment, but evidence of long-term clinical effectiveness was less strong. This appeared to be due to the patterns of clinical management in everyday practice. Patients tend to be treated with modest doses of hydroxycarbamide due to intolerance or inability to attain or maintain maximum tolerated dose. For example maximum tolerated dose was the aim of treatment for 91% of patients but it was achieved for 65% of participants. Non- compliance with treatment and monitoring schedule was the main reason for non- attainment.

Results suggest that it is sensible to strive for maximum tolerated dose to ensure therapy remains effective, but with more realistic expectations of the dose patients can attain and maintain. Doses in adult patients average 20mg/kg/day and 25mg/kg/day in children. Adult patients may be able to achieve a higher dose, if there was more stringent monitoring and improved management of non-compliance.

The North West London HU Sub-Registry proved useful for measuring long-term effectiveness and tolerability of hydroxycarbamide. Routinely collected data was utilized for both clinical management and research purposes. The novelty lay in examination of the nuances of routine clinical practice. An electronic patient record was developed as a clinical management tool. It is the first study reporting long-term outcomes for UK sickle cell disease patients on hydroxycarbamide.

Findings should help clinicians devise effective treatment protocols and strategies for managing patients commenced on this therapy. Interventions need to be targeted at increasing utilisation, patient adherence and persistence with treatment. The electronic patient record could be used to maximise treatment benefit and improve adherence. More effective involvement of the multidisciplinary team and primary care colleagues in patient education and management should improve usage. Patients and carers need up to date and easy to assimilate information to make informed decisions about treatment options.

Maintaining a SCD registry is challenging. Models which operate as clinical information systems provide an incentive for participation. These enable active involvement of local care providers in registry management and the ability to keep and utilize their own data. Clinicians require accurate and current data for patient management and to enable them to benchmark their local outcomes against national outcomes and care standards.

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Definitions of Key Terms

Disease register

A disease register is defined as a file of data concerning all cases of a particular disease in a defined population. Cases are regularly followed up and information on remissions, exacerbation, prevalence and survival can be obtained (Goldberg et al, 1980; Donaldson, 1992). The register is the actual document and the registry is the system of ongoing registration (Weddell, 1973) therefore it is possible for a registry to support several registers (Thompson, 1989).

Health technology

A health technology includes all methods used by health professionals to promote health, prevent and treat disease and to improve rehabilitation and long-term care (Dept of Health, 1992 cited in Raftery et al, 2005)). This definition includes different levels of interventions from organisational structures to individual components of healthcare including drugs (such as hydroxycarbamide), diagnostic tests and surgical procedures.

Incidence

Incidence rate is a measure of morbidity based on the number of new cases or episodes of illness arising in a population over an estimated period. It is expressed in terms of persons with the disease or episodes of the disease per 1000 individuals at risk.

Prevalence

The proportion of individuals in a defined population with a disease. Prevalence rate is a statistical concept referring to the number of cases of a disease that are present in a particular population at a given time (point prevalence) or over a stated period (period prevalence). It is expressed either as persons or episodes of sickness per 1000 individuals at risk.

List of Abbreviations

ACS Acute chest syndrome

AMI Acute myocardial Infarction

ANC Absolute neutrophil count

APACHE Acute Physiology and Chronic Health Evaluation

BSCTC Brent Sickle Cell & Thalassaemia Centre

C&W Chelsea & Westminster

CCAD Central Cardiac Audit Database

CCP Cooperative Cardiovascular Project

CEA Carotid Endarterectomy

CF Cystic Fibrosis

ChX Charing Cross

CMH Central Middlesex Hospital

CMP Case Mix Programme

CMPD Case Mix Programme Database

CONCORD Cancer survival in five continents: a worldwide population-based study

CPA Clinical Pathology Accreditation

CSL Chronic sickle lung

CVA Cerebrovascular accident

DARTS Diabetic Audit and Research in Tayside Scotland

DCDB Devon and Cornwall Database

DCO Death certificate only

DHR Danish Hip Arthroplasty Registry

DNA Deoxyribonucleic acid

DoCDat Directory of Clinical Databases

EGH Ealing General Hospital

EHR European Haemoglobinopathy Registry

EPR Electronic patient record

ERCF Epidemiologic Registry of Cystic Fibrosis

EUROCARE European Cancer Registries (co-operative project)

EuroSCORE European System for Cardiac Operative Risk Evaluation

FBC Full blood count

FinProg Finnish nation-wide breast cancer series (database)

Finnvasc Finnish Vascular (registry)

GP General Practitioner

Hamm Hammersmith

Hb Haemoglobin

HbA Adult haemoglobin

HbSβThal Haemoglobin S and beta thalassaemia trait

HbC Haemoglobin C

HbF Fetal haemoglobin

HCV Hepatitis C Virus

HPFH Hereditary Persistence of Fetal Haemoglobin

HPLC High performance liquid chromatography

HT Health technology

HU Hydroxyurea, now known as hydroxycarbamide

HUSOFT Hydroxyurea Safety and Organ Toxicity (trial)

ICD International Classification of Diseases

ICNARC Intensive Care National Audit & Research Centre

ICU Intensive Care Unit

IEF Iso-electric focusing

IP Inpatient

IT Information technology

IQR Inter-quartile range

LMP Last menstrual period

MCN Managed Clinical Network

MCV Mean cell volume

MEMO Medicines Monitoring Unit

MREC Multi-centre research ethics committee

MSH Multi-centre Study of Hydroxyurea

MTD Maximum tolerated dose

NCASP National Clinical Audit Support Programme

NCEPOD National Confidential Enquiry into Patient Outcome and Death

NHS National Health Service

NICR Northern Ireland Cancer Registry

NMSC Non-melanoma skin cancer

List of Abbreviations

NPH Northwick Park Hospital

NRMI National Registry of Myocardial Infarction

NRP National Register of Patients

NSF National Service Framework

NWL North West London

NYCRIS Northern and Yorkshire Cancer Registry

ONS Office National Statistics

OPCS Office of Population and Census Surveys

OPD Outpatient department

PAS Patient Administration System

PCT Primary Care Trust

PICU Paediatric Intensive Care Unit

PIN Personal identification number

PPV Positive predictive value

PROWESS Human Activated Protein C Worldwide Evaluation in Severe Sepsis (trial)

RBC Red blood cell

RCT Randomized controlled trial

REC Research ethics committee

Retic Reticulocyte

SCD Sickle Cell Disease

SCTS Society of Cardiothoracic Surgery of Great Britain and Ireland

SEER Surveillance, Epidemiology and End Results (tumour registries)

SMH Saint Mary's Hospital

SP Specialist

SWEDVASC Swedish Vascular Registry

TCR Trent Cancer Registry

THA Total hip arthroplasty

ThCR Thames Cancer Registry

Tx Transfusion

UKNACSD UK National Adult Cardiac Surgical Database

UKCFD UK Cystic Fibrosis Database

UKHVR UK Heart Valve Register

WBC White blood cell

List of Abbreviations

WHO World Health Organisation

WMUH West Middlesex University Hospital

Chapter 1: Overview of Sickle Cell Disease and Development of a Disease Registry.

1.1 Introduction

This chapter will describe the rationale for and aims of this thesis. It provides an introduction to sickle cell disease (SCD) and a history of medical progress in understanding and managing this serious chronic disorder in the UK. This is essential to understanding the origins of the SCD registry and the development of the research question to be answered by this study. The chapter sections are as follows: 1.2 describes the disease, 1.3 the epidemiology (1.3.1 incidence and prevalence and 1.3.2 disease detection methods), 1.4 the pathophysiology, 1.5 clinical presentation, 1.6 current management and survival, and 1.7 current treatments, especially hydroxycarbamide. Hydroxycarbamide treatment efficacy is discussed in 1.7.1, evidence of effectiveness in 1.7.2 and mechanisms of action which result in disease modification in SCD in section 1.7.3. Motivation for the development of a SCD registry is covered in section 1.8 including the history of the European Haemoglobinopathy Registry (1.8.1), rationale for developing an SCD registry (1.8.2) and origins of the present registry, the North West London sector Haemoglobinopathy Registry (1.8.3). The final section (1.9) describes the rationale for, aims, objectives and focus of this PhD study.

1.2 What is SCD?

Sickle cell disease is the name given to a group of inherited conditions that affect haemoglobin (Hb) formation in the blood. It is caused by an alteration of the beta globin gene which results in abnormal haemoglobin production. Haemoglobin is the oxygen carrying protein found in the red blood cells (RBCs). Adult haemoglobin (HbA) is the normal and most common type of haemoglobin seen in adults while newborn infants have predominantly fetal haemoglobin (HbF) which is largely replaced by adult haemoglobin by the age of one year (Oni et al, 2006; Sickle Cell Society, 2008). SCD occurs when an infant inherits the gene for sickle haemoglobin (HbS) from both parents or the gene for sickle haemoglobin from one parent and another abnormal haemoglobin gene, such as HbC or HbβThal, from the other parent (Brawley et al, 2008). The homozygous condition (HbSS), known as sickle cell anaemia, is the most common and most severe type of SCD

seen in the UK but the following clinically significant SCD genotypes are also common; sickle haemoglobin C disease (HbSC), sickle beta zero thalassaemia (HbS/β^0Thal), sickle beta plus thalassaemia (HbS/β^+Thal) and less frequently sickle haemoglobin D^{punjab} disease (HbSD^{punjab}) and sickle O^{arab} (HbSO^{arab}) (Panchan and Howard, 2005; Oni et al, 2006). Individuals who inherit only one sickle (HbS) gene from one parent and the normal HbA gene from the other are sickle cell carriers (HbAS): they rarely have clinical symptoms and often do not know they are carrying the HbS gene. However individuals with sickle trait are at risk of having children with a clinically significant syndrome if their partner also carries the sickle gene or another significant abnormal haemoglobin gene (Oni et al, 2006).

1.3 Epidemiology

1.3.1 Incidence and prevalence

The disorder occurs predominantly in individuals of African descent but these disorders are also prevalent throughout the Mediterranean, Middle East and parts of India, the Caribbean, and South and Central America (Sickle Cell Society, 2008). Due to population migration, there are people with SCD in most countries and because of the severity of the condition it forms an important part of health care practice. Early estimates suggested that sickle cell disease affected 1-2% (120,000) of infants in Africa annually but more recent data shows that there are more than 200,000 new cases per year (Davies and Oni, 1997; Strouse et al, 2008). About 50-60,000 people in the USA suffer from the disease and 2000 babies are born annually (Brawley et al, 2008; Platt, 2008).

There are at least 12,500 people living with the condition in England, where it is the most common and fastest growing genetic disorder (Hickman et al, 1999; NHS Sickle Cell and Thalassaemia Screening Programme, 2008). Recent data from the Newborn Screening Programme suggests that more than 300 babies with SCD and some 8,500 carriers are born each year (NHS Sickle Cell and Thalassaemia Screening Programme, 2008). Previous estimates by Hickman and colleagues (1999) reported that approximately 3000 babies (0.47%) born annually, in England, carried sickle cell trait, 2800 (0.44%) carried β thalassaemia trait and approximately 140-175 (0.22-0.28 per 1000) infants were born with SCD every year. Black ethnic minorities have comparatively high carrier rates of sickle

cell responsible for high rates of the disease: 5.6 per 1000 births among black Caribbeans and 14.7 among black Africans (Davies et al, 2000).

1.3.2 Disease detection

SCD is detectable from birth by a specialist blood test (Pancham and Howard, 2005; NHS Sickle Cell and Thalassaemia Screening Programme, 2006a). The test can be undertaken in the local haematology laboratory, provided it is CPA-accredited and takes part in quality control schemes for haemoglobin testing (NHS Sickle Cell and Thalassaemia Screening Programme, 2006a). Best practice in conducting and reporting screening tests are outlined in the 'Sickle Cell and Thalassaemia: Handbook for laboratories' (NHS Sickle Cell and Thalassaemia Screening Programme, 2006a).

The NHS Sickle Cell and Thalassaemia Programme was set up in 2001 as a result of the commitment, in the 'National Plan for England', to introduce effective antenatal and neonatal screening programmes for sickle cell and thalassaemia (Department of Health, 2000; NHS Sickle Cell and Thalassaemia Screening Programme, 2008). Consequently universal neonatal screening for sickle cell disease, using the Guthrie card system, was introduced in England in 2006. Antenatal screening programmes also identify a small proportion of adults with sickle cell. Individuals who have not been picked up by routine screening methods because they are immigrants or because they were born before screening was introduced are picked up in an ad hoc manner. Most common methods include family screening, presentation to the GP or local hospital with symptoms suggestive of SCD or during routine screening such as pre-operatively (Pancham and Howard, 2005).

1.4 Pathophysiology

There are two essential pathological processes: vaso-occlusion and haemolysis (Sickle Cell Society, 2008). Red blood cells (erythrocytes) are normally round and very flexible (see Figure 1.1) but when depleted of oxygen can become dehydrated and crescent shaped or 'sickled' in people with SCD. These deformed inflexible sickled red blood cells (see Figure 1.2) may not be able to pass through small blood vessels, tending to clump together and stick to blood vessel walls causing blockages and damage to the red cell membrane.

This phenomenon is called 'vaso-occlusion' and it may happen in any part of the body's microcirculation, resulting in extreme pain called a 'vaso-occlusive crisis' or 'painful crisis' in the affected part. The process prevents blood flow into the surrounding tissues and organs with deprivation of oxygen which may result in localised dying tissue and vascular damage leaving the organ permanently impaired. Large blood vessels are also damaged by this process, which may be the cause of such complications as stroke, acute chest syndrome (ACS) and pulmonary hypertension (Davies and Gilmore, 2003; Sickle Cell Society, 2008). Sickled RBCs have a shortened life span (16 – 20 days in contrast to 120 days in normal RBCs) due to the constant injury caused by these processes, which results in a chronic haemolytic anaemia. Individuals with SCD have an increased risk of serious infections due to non functioning spleens (functional asplenia) from repeated infarcts (Pancham and Howard, 2005).

| **Figure 1.1: Normal red blood cells** | **Figure 1.2: Sickled and other red blood cells** |
| Credit: David Gregory & Debbie Marshall | Credit: EM Unit/Royal Free Med. School |

1.5 Clinical presentation

The clinical syndrome results from chronic haemolytic anaemia, increased susceptibility to infection and vaso-occlusion, which in turn can give rise to chronic organ damage (Davies, 2003). The initial clinical presentation usually occurs in childhood but people with less severe SCD may not develop symptoms until later in life (Sickle Cell Society, 2008). The condition varies in severity from one person to the next for reasons that are not well understood (Oni et al, 2006). Known markers of severity include severe anaemia, a low haemoglobin F% (HbF%), dactylitis syndrome (hand/foot pain crisis) at a young age and

an increased white blood cell count (Davies, 2003). The most common clinical problem is painful crises which causes over 90% of acute hospital admissions and significant morbidity in the community (Brozovic et al, 1987; Fuggle et al, 1996; Ballas and Lusardi, 2005). Other common clinical conditions include overwhelming infection, ACS, lung disease, chronic leg ulcer, eye disease, kidney and spleen dysfunction, priapism and cerebrovascular accident (stroke) (Day and Wynn, 2000; Sickle Cell Society, 2008).

1.6 Clinical management and survival

Like other chronic diseases SCD is a major source of morbidity, mortality and health service resource utilization (Kahn, 1999; Steinberg, 1999). Affected people suffer unpredictable, potentially life threatening, acute adverse events which require precision clinical management for optimal outcomes (Department of Health, 1993). The chronic manifestations of the disease often occur insidiously thus requiring close monitoring to identify and treat complications early to prevent or arrest disease progression (Jones, 1998). Life expectancy is considerably reduced and death generally relates to SCD, caused either by chronic organ failure or as a result of an acute catastrophic event (Platt et al, 1994; Wierenga et al, 2001; Davies and Gilmore, 2003). A recent national confidential inquiry of sickle cell patient deaths in England reported that the most common causes of death in adults were cerebrovascular accidents (CVAs) and pulmonary complications (NCEPOD, 2008).

Up to 15 years ago management was, purely preventative and supportive, aimed at symptom control (Amrolia et al, 2003; Davies and Gilmore, 2003). Standard care involves lifelong infection prophylaxis and prevention of crisis. Treatment for acute uncomplicated pain crisis includes pain-killing medication, hydration and antibiotics (Davies and Gilmore, 2003). Life threatening crisis such as ACS may require transfusion of red blood cells and inhaled oxygen. Many patients need emotional, psychological, educational, employment and social support to cope as SCD can impact on every facet of life (Fuggle et al, 1996; Lee et al, 1997; Anie, 2005; Pancham and Howard, 2005). It is essential to have a multidisciplinary team approach which involves both primary and secondary care health professionals so that holistic care is provided to patients and their families (Pancham and Howard, 2005).

1.7 Available therapies

The only potential cure for SCD is stem cell transplantation, preferably from a matched sibling donor. There is still a sufficiently high risk of failure, complications and death from this procedure to preclude it as a mainstream therapy option in the UK (Davies and Gilmore, 2003; Chakrabarti, 2007; Darbyshire and Roberts, 2007). Long term red blood cell transfusion is the treatment of choice for secondary stroke prevention (Pancham and Howard, 2005; Sickle Cell Society, 2008). Due to the risks, complications and inconvenience of this therapy it is not widely used for other types of symptom control, for example pain crisis. Many drugs have been tested over the last 20 years but only hydroxycarbamide, previously known as hydroxyurea (HU), has proven efficacy in ameliorating the disease and improving life expectancy for most patients (Charache et al 1995; Davies and Gilmore, 2003; Steinberg et al, 2003).

1.7.1 Hydroxycarbamide: treatment efficacy

Charache et al (1995) showed conclusively in a large multi-centre double-blind randomized clinical trial, called the Multi-centre Study of Hydroxyurea (MSH), that adult patients treated with HU had statistically significant lower pain crisis rates than the placebo group. There were also significantly fewer patients on HU therapy that suffered an ACS episode or needed a blood transfusion. Weaker evidence suggests children have similar clinical benefits while on HU (Ferster et al, 1996; Hankins et al, 2005). In addition a nine year longitudinal observational follow-up of the original patient cohort in the MSH study showed a 40 percent reduction in mortality for those treated with HU (Steinberg et al, 2003).

1.7.2 Hydroxycarbamide: evidence of effectiveness in clinical practice

Despite this evidence there is still only a subset of potential patients who could benefit from HU being treated (Aliyu et al, 2005; Ballas and Lusardi, 2005; Lanzkron et al, 2006, Segal et al, 2008). A major problem is that the median length of follow-up is relatively short, thus weakening the evidence of long-term risk/benefit (Spell, 2003). Only a few studies have evaluated effectiveness of HU in everyday clinical practice. Ferster et al (2001) followed up a cohort of 91 children and young adults from the Belgium HU-treated

SCD registry for up to five years, with a median follow-up of 3.5 years. This prospective series was updated by Gulbis et al (2005), who reported the outcomes for 127 patients followed for up to eight years with a median of three yrs and 11 months. De Montalembert and colleagues (2006) followed up a French cohort of 225 SCD children and young adults with a mean duration of HU treatment of 3.8 years; ten had been on HU for over ten years. The other noteworthy study, by Steinberg et al (2003), followed-up the original MSH participants for up to nine years but most of the cohort received HU for less than 37 months (Spell, 2003).

Consequently little is known about the significance and magnitude of serious side effects with long term therapy. In particular the unquantified risk of patients developing leukaemia and the potential for HU to act as a teratogen has restricted usage (Davies and Gilmore, 2003; Zumberg et al, 2005; Hankins et al, 2007; Platt, 2008). No data exists pertaining to the proportion of sickle patients treated with HU therefore the relative incidence of serious adverse events is unknown (Halsey and Roberts, 2003). In addition ambivalence exists about which patients will benefit from treatment and how optimum benefit versus least risk can be achieved in routine clinical practice, outside the controlled environment of a clinical trial (Halsey and Roberts, 2003; Platt, 2008). For instance uncertainty prevails about why some patients are non responders, whether maximum tolerated dose (MTD) or a set dosing schedule is best practice, should the strict monitoring schedule be relaxed, and if clinical benefits are sustained in the long term (Davies and Gilmore, 2003; Segal et al, 2008).

Therefore insufficient evidence has made it impossible to convince the majority of patients, whom it could potentially benefit, to use it and their doctors to prescribe it.

1.7.3 Hydroxycarbamide: mechanism of action in management of SCD

The impact of HU was initially attributed to its ability to promote HbF synthesis, which is known to ameliorate the clinical symptoms of SCD. Recent research shows that it has many other beneficial effects which modify the clinical severity of the disease (Davies and Gilmore, 2003; Aliyu et al, 2005; Sickle Cell Society, 2008). These include improving red cell hydration, maintaining vascular tone, decreasing cytokine production and red cell adhesion. Davies and Gilmore (2003) provide a summary account of the reported mechanisms in which HU alleviates SCD symptoms.

1.8 Motivation to develop a sickle cell disease registry

1.8.1 History of European Haemoglobinopathy Registry

This ambivalence surrounding the long-term risks/ benefits of HU therapy led to close collaborations between the haematology department at Central Middlesex Hospital (CMH) and European partners which culminated in the development of a pilot European HU-treated SCD registry in 1998 (Davies and Roberts- Harwood, 1998). However this registry, called the European Haemoglobinopathy Registry (EHR), was discontinued for a number of reasons including loss of the co-ordinator, lack of funding and organisational difficulties. Subsequently a disease registry for all SCD patients was set up in its place, in 1999, with a special interest in monitoring the subgroup of patients treated with HU (Gilmore, 2001).

1.8.2 Establishing a disease registry for sickle cell

No other SCD registry existed and therefore this presented a unique opportunity to build upon the work and experience already gained from the original EU HU-treated SCD patient database. Furthermore recent government funded reviews of sickle cell services had advocated establishment of registries to help overcome the ongoing lack of accurate population based information and of research based evidence for effective patient management (Department of Health, 1993; Streetly et al, 1997). For example Zeuner and colleagues (1999) reported a virtual absence of UK epidemiological data for modelling predictions and estimations to determine the needs of a national screening programme for sickle cell disease.

CMH was the preferred location due to the high disease incidence and prevalence in the locality, the position of CMH as a specialist centre for patients with this condition and the high level of local enthusiasm and motivation for this project. In addition CMH had amassed critical expertise and infrastructure to establish and run the registry.

1.8.3 Origin of the North West London Sector Haemoglobinopathy Registry

The SCD registry was initiated at Central Middlesex hospital without any secure long-term funding therefore continual efforts were made, over the years, to attract funding in order to keep it viable. Survival depended on ad hoc streams of money to undertake various projects. Consequently, registry data collection and outputs were tailored to meet the requirements of the registry's sponsors. Initially a three year research grant was secured from the Department of Health, in 1999, to evaluate the long-term risk benefit of HU for SCD patients. A registry co-ordinator (the author) was employed to develop the registry. A further three year research grant was awarded, in 2002, to continue this study. Other sources of funding included a small grant from the Washington University School of Medicine, St Louis, Missouri. In addition funding from local health authorities (subsequently reorganised into Primary Care Trusts) was secured, in 2001, for three additional local hospitals to join the registry thereby expanding coverage to three-quarters of the SCD patient population in the local North West London Health Sector geographical region. This project was for three years. Further funding was not acquired to enable the remaining hospitals, in the sector, to participate or for the existing hospitals to continue in the registry from 2004. However Brent Primary Care Trust (PCT) continued to contribute to the running of the registry for CMH patients. This registry is known as the North West London (NWL) Sector Haemoglobinopathy registry and operates under the umbrella of the EHR.

1.9 Rationale for PhD

1.9.1 Feasibility of a successful registry

At this time there was plenty of debate about the desired components of a successful clinical registry (Thompson, 1989; Black, 1997) but little evidence or scrutiny of how they work in routine clinical practice settings. For instance many were still in their infancy, particularly in the UK, or had never been evaluated for reliability, efficiency and effectiveness (Rowan, 1996; Keogh et al, 1998; Black, 1999). This was not a trivial project as the opportunity cost of developing and maintaining a clinical registry is significant due to the complexity, resource requirements and longevity of the project (Thompson, 1989; Anionwu, 1997). The absence of evidence about the feasibility and utility of disease

registries led me, the researcher, to the conclusion that establishing and maintaining a sickle registry would need systematic investigation to identify the essential components to enable it to succeed.

1.9.2 The Research Question

The rationale for developing a sickle registry was to enhance the evidence base for SCD which in turn would benefit patient care. In particular urgent evaluation of the long-term effectiveness and safety of HU was required. Therefore it was necessary to test empirically if it was feasible to develop and sustain a 'successful registry'. The following hypotheses were proposed:

i. The development of a SCD registry for the dual purposes of patient clinical management and research is feasible.
ii. A SCD registry will provide tangible benefits to SCD patients, their health care providers and the wider health community.

1.9.3 The Aim

The aim of this thesis is to evaluate the feasibility and utility of a SCD registry for clinical management of patients and research.

1.9.4 The Objectives

       i. Develop an evidence based registry

       ii. Assure high quality data

       iii. Develop clinical management tools from the registry data

       iv. Demonstrate utility of the registry for SCD patient management and research

1.9.5 Focus of PhD study

This evaluation will be focused, mainly, on the hydroxycarbamide sub-registry as it provides a distinct subsection where the topic and study population are easily defined and investigation of HU usage for SCD patients is critical.

Chapter 2: Review of the Literature

2.1 Introduction

This literature review will identify the main issues to be considered when establishing a clinical database or disease registry. The phrases 'clinical database' and 'disease registry' are used interchangeably throughout as the literature does not tend to differentiate between the two and some electronic databases function as both disease registries and clinical databases. A model that serves as both a disease register and clinical database appears to be the most suitable for sickle cell disease (SCD).

The North West London Sector Haemoglobinopathy registry is managed by National Health Service (NHS) employees, in an NHS facility, and participants receive their healthcare from the NHS. Studies that are conducted in environments with the same or similar health services are likely to identify relevant problems and provide better insight of the critical attributes necessary for a successful sickle cell disease registry in North West London. Therefore the focus will be on British and European literature and additional studies will be included if they add value to the review.

2.1.1 Background

Clinical database and disease registry outputs are increasingly used to assess quality of care and for epidemiological and health service research in the UK (Black, 1999; Brewster et al 2002). In addition database outputs can be utilized in routine clinical management to help patients and their clinicians decide on their best treatment and care options, however this function is unproven (Black, 2003a). Nevertheless they remain under utilized and often regarded with scepticism because until recently there was little known about which databases actually existed in the UK and even less about their scope, remit and quality (Black and Payne, 2002).

In an attempt to address the paucity of information Black and colleagues developed a web based Directory of Clinical Databases called DoCDat, which aimed to list all UK multi-centre clinical databases together with an independent assessment of their scope and quality (Black and Payne, 2003; Black et al, 2004). The directory was populated with

information on 105 databases and they found that the audit and research potential of most databases had not been realised (Black et al, 2004). This concurs with Raftery et al (2005) who evaluated English databases and found that their main use was for comparative audit.

A major factor in this underutilization is likely to be due to uncertainty about the quality of data held in databases (Keogh et al, 1998; Black and Payne, 2003; Fine et al, 2003; Keogh et al, 2004). Contents of the database must be seen to be valid and reliable for confidence in its outputs and this assessment of quality will determine what uses can be made of it (Black and Payne, 2003; Fine et al, 2003). The most important dimensions when assessing quality are completeness and accuracy (Black and Payne, 2003). Black and Payne (2003) constructed and tested an instrument to objectively evaluate the quality of databases, which included the assessment of coverage, reliability and validity. The authors assert that these dimensions cover all methodological threats to the reliability, internal validity and external validity/generalisability of a database.

Strict regulations govern the operation of clinical databases/ registries as they usually hold personal health data and therefore must comply with the Data Protection Act 1998, the Common Law of Confidentiality, Human Rights Act 1998 and Administrative Law (Department of Health, 2003). Custodians are obliged to ensure patient privacy and respect without jeopardising the methodological integrity of research and audit derived from the data (Al-Shahi and Warlow, 2000; Black, 2003b; Fraser, 2003; Lowrance, 2003; Willison, 2003).

This project already has multi-centre research ethics committee approval with the condition that informed written consent (opt-in consent process) will be gained from all patients prior to utilization of the data for research purposes. Acquiring consent is not a trivial matter and rates are affected by the cumulative effect of barriers to accessing and approaching eligible patients as well as gaining consent. The credibility and generalisibility of results from observational research may be affected if the excluded non-consented patients are systematically different to the consented cohort in characteristics that matter (Woolf et al, 2000; Verity and Nicoll, 2002; Tu et al, 2004; Al-Shahi et al, 2005).

In addition the complexity of running a registry and sustained efforts and resources required to keep it viable often result in underutilization or termination (Thompson, 1989;

Donaldson, 1992). However there are some recent examples of successful databases where sustained efforts, resources and political drive have ensured their survival. For instance the long established cardiac surgery and cancer databases have thrived over the last decade due to support derived from government policy initiatives. These policies aimed to improve quality of health care and promote active involvement of patients in health care decision making processes. For instance the cardiac surgery databases have been greatly supported by the national service framework (NSF) for coronary artery disease, launched in 2000, and the Central Cardiac Audit Database (CCAD) project. CCAD is part of the National Clinical Audit Support Programme (NCASP) (Keogh et al, 2004).

At the core of these initiatives were plans to ensure that information in the NHS could be transferred seamlessly across sectors; the task was designated to the NHS Information Authority (now known as NHS Connecting for Health). NCASP, a component of the NHS Information authority, was responsible for promoting clinical audit in cancer and coronary heart disease. The goal was to harmonise data collection between cardiology, cardiac surgery and other administrative systems so that everyone had ownership of, and was working from, the same base dataset and the same definitions (Keogh et al, 2004).

The UK regional cancer registries are another example of how government influence and support helped to improve these registries. Reliable population based information derived from cancer registries were viewed as essential to the implementation and monitoring of 'the NHS Cancer Plan', in 2000. This document was the driver to reforms in the UK cancer services. Integral to these reforms were schemes to improve the national cancer datasets, outlined in the 2000 Cancer Information Strategy (Department of Health, 2008).

In conclusion the issues to be considered when developing a clinical database/ disease registry are the purpose, organisation and quality assurance processes involved. The literature will be appraised to identify and quantify these critical aspects of establishing a successful disease registry for SCD patients. Finally how do we know if the registry is effective? Registries are thought to benefit patients, their health care providers and government agencies involved in the planning and funding of health services. Therefore the utility of existing registries will be evaluated to determine how to maximise the potential of a SCD registry.

2.1.2 Chapter structure

The next section (2.2.) reviews the purposes and benefits of clinical registries/ databases. This is outlined as follows: Section 2.2.1 explores the properties and purpose of different types of clinical databases to identify a feasible model for SCD and Section 2.2.2 will evaluate the scope and usefulness of existing clinical registers. Section 2.2.3 reviews registries for chronic diseases; Section 2.2.4 databases set up to evaluate health technologies; and section 2.2.5 cancer registries.

Section 2.3 covers the pertinent legal and ethical topics relating to clinical registries. These include data storage and use (section 2.3.1), personal identifiers (2.3.2), requirement for patient consent (2.3.3), consent process (2.3.4), consent bias in population health surveys (2.3.5) and consent bias in clinical registries (2.3.6).

Section, 2.4, reviews the quality issues pertaining to registries. Section 2.4.1 summarises the origins of registry data, 2.4.2 examines the need for validation, 2.4.3 covers the reliability of data abstraction and 2.4.4 timing of data. The topics relevant to registry completeness are explored next: section 2.4.5 explains completeness in the context of a database, 2.4.6 examines completeness of follow-up, 2.4.7 completeness of case ascertainment, 2.4.8 timeliness of case ascertainment, 2.4.9 geographical coverage and the value of indirect quality indicators are reviewed in section 2.4.10.

Findings are summarised in the discussion (section 2.5) and conclusions under 2.6.

2.2 Purposes and benefits of clinical databases and disease registries

2.2.1 Deciding on a model

Raftery et al (2005) classified English databases in terms of their usefulness in health technology (HT) assessment. This classification system is useful in deciding the properties for a sickle cell disease registry. Their system distinguished between three groups of databases: those with both HT and patients' characteristics, and those with one or the other of these. Their findings suggest that databases able to assess effectiveness, diffusion and

equity include information on both a HT and patient characteristics. Health state data must be collected at the level of individual patients to be useful.

Clinical registries were considered the best source of data on HT and patient health states. These are either designed around gathering data on the recipients of a health technology, such as the databases concerned with a specific surgical intervention or a drug, or around an entire client or disease group. However registries that only cover a HT do not include all the patients with the health condition so their uses are limited to comparative audit. Registries that cover the entire client or disease group are the most effective at assessing effectiveness and equity because they include all individuals with the common factor (i.e. disease), whether they received the HT or not.

In contrast clinical-administrative databases tend to have less depth but greater breadth of coverage than clinical registries as they were originally designed for administrative purposes. They contain some patient level information including identity, treatment and some health state or outcome data (Raftery et al, 2005). Examples include the Hospital Episode Statistics, the General Practice Research Database and cancer registers. They are of limited use in terms of measuring HT effectiveness except for the cancer registries, which can measure comparative mortality. These databases also have the potential to measure equity and diffusion because of their good coverage. Raftery and colleagues (2005) suggest that cancer registries have limited data on HTs but could include more variables to be clinically richer like disease registries.

Clinical registries/ databases and cancer registries appear to have all the relevant properties and potential uses needed for sickle cell patients; therefore these types of registries will be the focus of this literature review.

2.2.2. Scope and uses of clinical disease registries and health technology databases

A wide range of clinical areas have databases but this review will focus on the categories of databases the author perceives could fit with the care and management of SCD patients. Section 2.2.3 will evaluate registries set up to monitor patients with serious and clinically significant chronic diseases, similar to SCD. Section 2.2.4 will explore databases set up to

evaluate health technologies as any registry will require the ability to evaluate the effectiveness of existing and future health technologies for SCD. As stated in chapter 1, hydroxycarbamide use in SCD requires monitoring and evaluation and therefore this will be a priority for the database. Section 2.2.5 will review cancer registries as they are the most prolific registries in the UK; are well established and funded; and mandated by national and European governments as an essential population based information resource. It is hoped the experiences of these registries will give valuable insight into how to use and manage a SCD registry.

2.2.3 Chronic disease registries

2.2.3.1 Cystic Fibrosis

The chronic disease register for cystic fibrosis called the UK Cystic Fibrosis Database (UKCFD) commenced in 1992 as an audit project to establish the number and characteristics of the Scottish cystic fibrosis (CF) population and subsequently evolved into a clinical database by collecting additional variables on disease severity (Mehta et al, 2004). It gradually expanded in terms of remit, mode of operation and coverage and now covers most of the UK cystic fibrosis population. Its multiple functions are purported to benefit CF sufferers, their health care providers and government agencies. For example participating clinics are able to produce individual patient reports from their registry data which support clinical management during patient consultations. These reports provide feedback to the patients on relevant aspects of their disease and care. Mehta et al (2004) purport that the benefit derived from this feature encourages clinicians to continue to collect data for the registry. Over time clinicians requested more detailed clinical reports which proved the derived benefit of the database as a clinical management tool (Mehta et al, 2004).

Information from the UKCFD has been used by the Scottish NHS for budget planning as the registry can profile the current and future CF population. This information is purported to be useful for planning the location of new clinics, calculating staffing needs and disease burden in terms of lung disease. For example by constructing disease severity scores they have been able to band patients into 'cost categories'. The aggregate data has also provided valuable information for national audit. Examples include profiling drug usage which has highlighted clinics that prescribe potentially toxic drug dosages and inter-clinic

comparisons that have identified the prevalence of poor nutritional status of children in CF clinics. These serious deviations from optimal care standards were fed back to individual clinics for remedial action and stimulated debate among clinicians and research initiatives to identify causal factors. Published studies from the database include investigation of clinical outcomes in CF disease such as reproductive prognosis (Boyd et al, 2004); risk factors for increased morbidity (Sims et al, 2005a); and evaluation of health programs such as newborn screening for CF (Sims et al, 2005b, c).

In addition the registry can identify potential subjects for research into the CF gene. Mehta and colleagues (2004) suggest the registry already assists clinical trials by assigning controls for cluster case control studies and providing information on anticipated patient numbers for randomized trials.

2.2.3.2 Diabetes

Traditionally diabetic registers were used to assess incidence and prevalence of diabetic patients in local communities and were derived from aggregating diabetic patient records held in general practices (GPs) or by integrating GP registers with lists of patients who attended hospital diabetic clinics (Burnett et al, 1992; Morris et al, 1997; Gill et al, 2003). More recently some registers have expanded their remit and are used to conduct research. For example the 'Diabetic Audit and Research in Tayside Scotland' (DARTS) database has been used extensively to evaluate health technologies, the effects of the disease on morbidity, mortality and identification of risk factors (Evans et al 1999, Evans et al, 2002, Evans et al, 2005, Tan et al, 2004). DARTS data has also been combined with other validated health databases using cross sectional and cohort methodologies. For example Evans et al (1999) combined data from DARTS with the Medicines Monitoring Unit (MEMO) dispensed prescribing database to investigate patterns of self monitoring of blood glucose concentration in insulin dependent diabetic patients. Another study compared risks of cardiovascular outcomes between patients with type 2 diabetes and patients with established coronary heart disease using DARTS data in combination with inpatient hospital admissions and death certificate data (Evans et al, 2002).

2.2.3.3 Hepatitis C

Another UK chronic disease registry, called the National Hepatitis C Virus (HCV) Register, aims to document the natural history of hepatitis C infection in a cohort of UK patients (Harris et al, 2000). To date the registry has proved useful in epidemiological and evaluative research and as a national audit tool in care provision. For example registry data has been used to document the clinical course of hepatitis C virus in the first 10 years following infection (Harris et al, 2002) and to describe survival rates and predictors of survival (Harris et al, 2006). Brant et al (2005) have used the data to demonstrate the care pathways for these patients and evaluate resource utilization. The authors were able to compare actual care with national policy recommendations. Findings highlighted deviations from recommended patient management and treatment and identified care providers not following the recommended care pathways. The authors also profiled the usage of antiviral drug treatments, in this cohort, assessed response rates and identified factors affecting effectiveness of treatment regimes.

2.2.4 Health Technology Databases

2.2.4.1 UK Cardiac Surgical Register

The first UK cardiac surgical register was set up in 1977 with the aim of improving standards of care (English et al, 1984). It was the first attempt by any medical speciality in Britain to collect national activity and outcome data. It provided the first national information on trends in incidence of and mortality from cardiac surgery. The data was collected at the level of the 'cardiac unit' and all the information was presented in completely anonymous aggregate form in the annual report. Individual units and surgeons received an annual report. The objective was to enable each surgeon to compare his or her performance with the national trends and encourage local introspection and action (Keogh et al, 1998). Additionally this data provided the first analysis of regional workloads so policy makers were able to plan services and target resources where they were needed.

2.2.4.2 UK Heart Valve Registry

The establishment of other registries for cardiac surgery followed, including the 'United Kingdom Heart Valve Registry' (UKHVR), in 1986 (Taylor, 1997). The additional benefit of this registry was the ability to provide actuarial survival data for valve replacement

surgery as it was linked with the Office for National Statistics (ONS) for the provision of mortality data. If any UKHVR patient died the ONS sent a copy of the death certificate to the registry which enabled comprehensive and accurate data for early mortality (up to 30 days post operative) and for longitudinal survival analysis. The UKHVR also provided an important regulatory role as it collected the serial number of each implanted valve which could be used for monitoring safety and evaluating performance of individual valves.

2.2.4.3 UK National Adult Cardiac Surgical Database

A major development was the establishment of the UK National Adult Cardiac Surgical Database (UKNACSD), in 1994, which ran in parallel with the UK Cardiac Surgical Register (Keogh et al, 1998). This database collected an expanded dataset including patient specific information on co-morbidity for case-mix analysis to enable comparative audit (Keogh et al, 1998; Keogh and Kinsman, 2001; Keogh et al, 2004). The first surgeon specific crude unadjusted mortality figures were published in 2004 (Keogh and Kinsman, 2004). This data was of insufficient quality to compare each surgeon's performance but it could assess safety by identifying any surgeon's performance that lay outside a predefined mortality limit (Keogh et al, 2004).

2.2.4.4 North West of England Regional Cardiac Database

In contrast the North West of England Regional Cardiac Database managed to use their data for comparative audit of surgeon's post operative mortality (Bridgewater, et al 2003; Bridgewater, 2005). These authors were able to use the data to compare death rates between individual surgeons following adult cardiac surgery, stratified by risk (low and high risk patients). Bridgewater (2005) was able to demonstrate that risk stratified data was a good and fair indicator of a surgeon's performance. This was the first data analysis that could be used to monitor a surgeon's performance and enable patients to make informed choices about their cardiac surgery. It was essential to produce good quality risk stratified information that had the confidence of surgeons to avoid risk adverse behaviour. For example surgeons would avoid operating on high risk patients for fear of bad outcomes, which are much more likely in high risk cases. If the analysis of outcomes could not adequately adjust for a surgeon's case mix this could give an unfair assessment of the surgeon's results and adversely affect their performance in the government 'league tables' (Keogh and Kinsman, 2001; Bridgewater et al, 2003).

2.2.4.5 Central Cardiac Audit Database

Under the national service agreement for coronary heart disease (2000) data collection from the UK National Adult Cardiac Surgical Database shifted to the Central Cardiac Audit Database (CCAD) in 2003 (Keogh et al, 2004; Keogh and Kinsman, 2004). An added value from this move was the ability to track deaths from the ONS. According to Keogh and colleagues (2004) this would enable future analysis of factors that influence long-term survival in addition to the current focus on early post operative death.

Since the move to CCAD the database has developed further and the data is now risk adjusted so that accurate comparisons can be made against national and international survival rates as well as between surgeons. Outputs from CCAD are now available for review via a public website (Healthcare Commission, 2008). The public can get current reliable information about the rates of post operative survival from cardiac surgery for individual surgeons and hospitals in the UK. The data has also been used to develop an interactive tool for the website which enables patients' to calculate their predicted survival rate post surgery.

Keogh and Kinsman (2004) suggested the current comprehensive dataset would enable other performance indicators to be measured including complication rates and length of stay. The aim was to move beyond the basic outcome measure of post operative hospital mortality rates to better and more sensitive outcomes and quality of practice indicators. For instance risk of stroke may be equally or even more important to the patient than risk of death following surgery (Keogh and Kinsman, 2004).

2.2.4.6 Intensive Care National Audit & Research Centre Case Mix Programme Database

The Intensive Care National Audit & Research Centre (ICNARC) coordinates a national comparative audit of patient outcomes from adult, general critical care units in England, Wales and Northern Ireland called the Case Mix Programme (CMP) (Rowan, 1996). Their database 'The Case Mix Programme Database' (CMPD) has been used extensively for research as well as audit purposes. Using the criteria of Raftery et al (2005) the database is classified as describing a health technology. Units submitting data receive comparative data analysis reports from which they can identify their own unit's performance compared

with all other participating units. Clinicians and managers can also interrogate the CMPD directly by submitting requests for analyses to ICNARC (Harrison et al, 2004).

Initial research from the CMPD provided reliable baseline information on the case mix, outcome and activity of patients admitted to intensive care units (ICUs) (Harrison et al, 2004). Other studies looked at outcomes for specific patient groups including the influence of patient gender on admission to ICU (Raine et al, 2002), influence of night discharge from ICU on patient mortality (Goldfrad and Rowan, 2000), comparative outcome analysis of patients admitted with end stage renal failure (Hutchison et al, 2007) and epidemiology of severe sepsis in ICUs (Padkin et al, 2001; Padkin et al, 2003). Over time the utility of the CMPD has increased as comprehensive data has been collected, year on year, since 1996 and more ICUs have joined thereby increasing national coverage. This enabled examination of yearly trends in the incidence of and mortality from severe sepsis (Harrison et al, 2006).

The CMP database has also been used to identify potential ICUs for participation in further research studies (Wildman et al, 2007). The study by Wildman and colleagues (2007) is a practical example of the versatility of the database and also the potential cost efficiencies if this type of data repository is fully exploited. These researchers conducted independent research, involving interviews with ICU consultants, and then supplemented the information with routinely collected outcome data from the CMPD.

The strength of the CMPD derives from its ability to collect information in an on going and systematic fashion and therefore the results reflect what is happening in actual clinical practice. Results identify issues for further action or investigation. This follow through is required if the database is to be of benefit to patient care. For example it is known that ICUs have been very slow to implement the results of clinical trials that have proven efficacy in reducing mortality in patients admitted with severe sepsis (Dellinger and Vincent, 2005; Harrison et al, 2006). Clinical guidelines and 'care bundles' were developed for this condition in an effort to implement changes to patient care and management. A care bundle is a group of interventions to help clinicians change practice in line with evidence based interventions (Dellinger and Vincent, 2005). Harrison and colleagues (2006) purport that the results of their study provides essential baseline information for future evaluation of the impact of these care bundles on patient outcomes.

The CMPD could also be used to test the generalisability of the results of randomized controlled trials (RCTs) and to assess the financial implications of introducing new treatments (Padkin et al, 2001). An example is the recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial which assessed the effectiveness of this treatment for severe sepsis. Randomized controlled trials are often preformed in atypical settings with atypical patients, making it difficult to assess the applicability of the results (Padkin et al, 2001). Therefore, even if the evaluated intervention provides significant benefit for the patients studied, clinicians have to make their own judgment about which patients will benefit, if any, in routine clinical practice. The authors suggest that the CMPD could follow-up patients which are prescribed new mediciations, such as recombinant Human Activated Protein C, longitudinally after clinical trials are completed. This would enable monitoring diffusion of the new drugs and assessment of their long-term effectiveness in clinical settings. The advantages of using a pre existing system like the CMPD are its wide coverage, high quality, data collection systems already exist and participating clinicians are familiar with the database systems (Padkin et al, 2001).

2.2.4.7 European Vascular Surgery Registries

The Nordic countries have had vascular surgery registries for the last 20 years and these have been operating on a national basis for the last 10-15 years. Data from the registries are utilized extensively for evaluative and epidemiological research and audit including national audits, to determine incidence of various vascular surgeries, to assess operative risk and incidence of surgical complications, and to compare national surgery outcomes with those achieved by randomized controlled trials (Bjorck et al, 1996; Kantonen et al, 1997a; Kantonen et al, 1998; Kragsterman et al, 2004; Laustsen et al, 2004). For example Kragsterman et al (2004) used data from the Swedish Vascular Registry (Swedvasc) to audit complication rates after Carotid Endarterectomy (CEA) surgery. Using a combination of cohort and case-control designs the authors were able to identify risk factors for serious complications (i.e. death and permanent stroke), to quantify the complication rate and compare performance of the different types of centres performing CEA surgery. Findings showed university hospitals as an independent risk factor for serious post operative

complications but not enough information was collected to understand why outcomes were worse in this category of hospital.

2.2.4.8 Belgium HU-treated Sickle Cell Disease Registry

A national registry for hydroxycarbamide (HU) - treated sickle cell disease patients was established in Belgium in 1996 under the auspices of the Belgium Society of Hematology (Ferster et al, 2001). It was set up to collect prospective longitudinal clinical data on children and young adults treated with HU to evaluate the drug's long-term efficacy and toxicity. The HU clinical benefits in adults with severe SCD had been confirmed by a large multi-centre RCT in 1995 (Charache et al, 1995) but evidence of the drug's efficacy in children was weak (Ferster et al, 1996; Ferster et al, 2001). Furthermore the treatment's effectiveness and safety in the median and long-term was unknown (Ferster et al, 2001).

Registry findings were published after five and eight years follow-up (Ferster et al, 2001, Gulbis et al, 2005). This follow up of patients enabled the everyday clinical use of this treatment for sickle patients in Belgium to be profiled. Findings provided an insight into some of the problems with long-term therapy such as non-adherence to treatment regime and management protocol, long-term effectiveness, reported side effects and therapy attrition. In addition American researchers were able to compare outcomes of the Belgium cohort with their own to give better insight into the usability and sustainability of HU in the median to long-term (Zimmerman et al, 2004).

2.2.4.9 Epidemiologic Registry of Cystic Fibrosis (ERCF)

This was a European wide multicentre, longitudinal follow-up project of the long-term effectiveness and cost effectiveness of the drug 'dornase alfa' for cystic fibrosis patients (Strobl et al, 2003). A randomized control trial had observed a treatment benefit with up to 96 weeks of use (Quan et al, 2001) and a Cochrane review showed that the drug seemed to be effective for up to six months (Jones et al, 2003). Longer term follow-up was required to undertake an economic evaluation of usage. Clinically rich data on the health technology and on patient health states were collected to make longitudinal comparisons between patients taking the drug and those not taking it.

2.2.5 Cancer registries

2.2.5.1 UK Regional and National cancer registries

In Great Britain national and regional cancer registries are the most prolific types of databases in operation, with 11 general and 14 specialized cancer databases included in DoCDat (Black et al, 2004). Cancer registration in England is conducted by nine regional registries and Scotland, Wales and Northern Ireland have their own registries (Micheli et al, 2003). Many of these regional registries were established in the 1950's and have been supplying data to the Office of National Statistics (previously called the Office of Population and Census Surveys (OPCS)) since the early 1960's, for the provision of national cancer statistics (Department of Health, 2008). Cancer registries are viewed as essential to the implementation and monitoring of key national initiatives, such as the NHS Cancer Plan (2000) and the more recent Cancer Reform Strategy (2007), which aim to improve the quality of care and survival for cancer patients. The aim is to enable timely, comparable, high-quality data for comparative audit and research. Trend data has shown the progress in cancer survival over the last decade so that the government is able to measure if reduction in mortality is in line with policy targets (Department of Health, 2007a). Other findings show poorer outcomes for some groups of patients, suggesting inequalities in care and services. The results have enabled the Cancer Reform Strategy (2007) to target initiatives, funding and services where they are most needed to improve outcomes for patients (Department of Health, 2007a). Registry data has also been linked with other NHS services to evaluate their effectiveness. It is purported that feedback on service quality to service providers of the national breast and cervical screening programmes has resulted in year on year improvement in services (Department of Health, 2007a). Cancer registries assist external research by supplying patient names to bona fide researchers for projects investigating causes of (and outcomes from) specific cancers.

There is evidence that regional registries can utilize their own data to improve patient care and outcomes locally. For instance Silcocks et al (1999) used data from a UK regional prostate cancer registry to audit clinical care and investigate the possibility of identifying surrogate variables to assess quality of care. The results identified deficiencies in clinical practice and made recommendations for standardization and quality assurance in the content of pathology reports and for standard treatment protocols to assist with recording

and comparison of treatments. They also found that only 2% of patients were recruited to RCTs.

In addition the majority of UK cancer registries contribute data to international publications and European studies such as EUROCARE.

2.2.5.2 EUROCARE

The European Cancer Registries (EUROCARE) co-operative project was set up in 1989 to measure and explain international differences in cancer survival in Europe (Coleman et al, 2003). It is the largest population- based cancer registry study on survival in European cancer patients (Micheli et al, 2003). The initial project was developed further with the EUROCARE 2 study, then EUROCARE 3 and recently the results of EUROCARE 4 have been published (Berrino et al, 1998; Coleman et al, 2003; Berrino et al, 2007). By 2003 this project had led to over 100 published papers exploring survival patterns for individual cancers (Coleman et al, 2003). An important outcome of EUROCARE is the ability to measure differences in survival from cancer over time and between and within European countries. (Berrino et al, 1998; Coleman et al, 2003; Richards, 2007). These results continue to be used as a reference point for individual countries to compare their relative survival rates for specific cancer sites (Angell-Andersen et al, 2003; Berrino et al, 2007; Department of Health, 2007a; Richards, 2007).

The sustained efforts to improve the quality and range of data collected by the registries which populate the EUROCARE have enhanced the utility of this database. Analysis of data has progressed from identification of a problem to, in many cases, understanding why the problem occurred so that corrective action can be taken. For example the researchers were able to use the data in conjunction with macro-economic variables to assess the relationship between better cancer outcomes and each country's wealth and level of health expenditure (Micheli et al, 2003). In addition 'high resolution studies' were conducted on subsets of patients to try and explain inter country differences in survival (Gatta et al, 2000; Sant et al, 2003; Sant et al, 2007). This was achieved by gathering more detailed data on diagnostic and treatment procedures from a representative sample of incidence cases in areas where the analysis identified extremes in survival rates.

EUROCARE results were one of the major influences in shaping UK national policies and practices in cancer care subsequent to the Calman- Hine Report (1995)(Department of Health, 2007a; Richards, 2007). Results showed that while UK survival rates for most cancers were improving over time they persistently lagged behind other comparable developed European countries (Coleman et al, 2003, Micheli et al 2003). The high-resolution studies indicated that UK outcomes were comparatively worse mainly due to patients being diagnosed at a more advanced stage of the disease. These results had a major influence on the development of the English NHS Cancer Plan (2000) (Richards, 2007). For example findings were able to inform policymakers that service changes were required to enable earlier cancer diagnosis. The latest results, from EUROCARE 4, were used as an indicator of NHS performance in cancer care and treatment and to measure the effectiveness of the NHS cancer plan reforms (Berrino et al, 2007; Department of Health, 2007a; Richards, 2007; Verdecchia et al, 2007).

EUROCARE has continued to be progressive, innovative and increasingly collaborative. For instance EUROCARE survival data has been compared with survival data from the cancer registries covered by the Surveillance, Epidemiology, and End Results (SEER) databases of the United States (Gatta et al, 2003; Verdecchia et al, 2007; Sant et al 2008). EUROCARE also collaborates with other cancer registries worldwide to expand comparisons to other populations in developed countries (the CONCORD project) (Berrino, 2003; Coleman et al, 2008). This project has enabled direct comparison of cancer survival between high-income and low-income countries and results may act as a stimulus for change. Coleman and colleagues (2008) suggest that these findings should eventually facilitate joint assessment of international trends in incidence, survival and mortality as indicators of cancer control.

The longevity of the cancer registry datasets has enabled statistical methods to be developed and tested for making predictions and estimations. For example Brenner et al (2002) used the long-term series of the Finnish cancer registry to test the accuracy of a new method of predicting long-term survival called period-analysis. The method was applied to the EUROCARE-4 series to enable more up-to-date survival information to be reported then was previously available (Richards, 2007). The improved timeliness of the data made the findings more relevant for assessing the performance of current healthcare services and practices. Similarly cardiac datasets have enabled risk measurement instruments, such as

Parsonnet and EuroSCORE, to be developed and tested for accurate prediction of cardiac surgery outcome (Keogh and Kinsman, 2001).

2.2.5.3 FinProg Breast Cancer Series

Lundin et al (2003) report on an interactive web based decision support system that was developed to generate survival estimates, in real time, using existing cancer survival data. This case-match survival estimation system was applied to the FinProg breast cancer dataset of women diagnosed with breast cancer in Finland in 1991-2. This system allows clinicians to estimate survival based on actual data for the entire available follow-up period, in this case 10 years, and not just a single time point estimate. A clinician can obtain a prediction of survival for a new patient by matching her disease profile to that of all previous patients with the same profile whose outcome is known. The system can be applied to any clinical database that holds data on patient characteristics that affect outcome and time to event information. These techniques can promote patient centred care and enhance shared clinical decision making between clinician and patient (Black, 2003a). It is also purported to increase the accessibility of the anonymised datasets to clinicians and researchers creating a climate of openness and sharing. However the robustness and accuracy of the estimates depends on the quality of the underlying data set (Lundin et al, 2003). Secondly clinical care changes over time therefore the data would need to be more contemporary to give an accurate prediction of survival (Black, 2003a).

2.3 Legal and ethical perspectives

Important issues relating to data confidentiality, security and consent have evolved with the increasing use of databases for managing patient care, audit and research. Custodians are obliged to ensure patient privacy and respect without jeopardising the methodological integrity of research and audit derived from the data (Al-Shahi and Warlow, 2000; Black, 2003b; Fraser, 2003; Lowrance, 2003; Willison, 2003). In the first instance data security and patient confidentiality procedures are required for the physical processes of collection, transmission and storage of personal data. Then additional confidentiality measures are required to use it for research and audit. Finally there are the ethical, legal and practical implications of ensuring that patients know about and have consented to the secondary use of their health information for these purposes.

2.3.1 Patient data storage and use

Health databases used for secondary research have two interrelated functions (Lowrance, 2003). They receive, store and safeguard data and they are also the providers of data for research and audit to internal and/or external researchers. Lowrance (2003) suggests that 'stewardship' adequately describes the responsibility of the custodians of a health database as it infers the notion of judicious protecting and sharing. In the UK the collection, storage and processing of identifiable patient information is governed by The Data Protection Act 1998 which came into force on 1 March 2000. The purpose, content and length of storage of all personal data must be justified by all agencies holding personal data and the confidentiality of data held is paramount. The guiding principle is that if an item of personal data is not essential to the purpose then it should not be held.

2.3.2 Patient identifiers

A requirement of any longitudinal cohort study is the ability to link participant's data over time. This facilitates completeness of recruitment; avoids duplicate entries; enables follow-up; and analysis of trends over time (Black, 2003b). A range of procedures are used by registries to enable longitudinal linkage while maintaining patient privacy. In the UK Cystic Fibrosis Database model the patient information is anonymised before it is stored in the database (Mehta et al, 2004). The computer generates a unique personal identification number (PIN) for each new patient registered which cannot be reverse-engineered. This PIN is then used as the identifier for all data entered into the database concerning that patient. This serves to maintain patient privacy and at the same time tags all the patient's records. Paper forms identifying patients are kept securely in a locked room centrally. Similarly national and regional cancer registries send datasets with an anonymous PIN for each case to EUROCARE. In addition the day of the month is removed from all dates attached to patient information which improves confidentiality without compromising the utility of the data (Berrino et al, 1998). Another example of compliance with patient privacy regulation is the method employed by the Finnish Vascular registry (Finnvasc). In this national registry the patient identification variables are permitted in the local site registries but removed prior to mailing to the central registry (Kantonen et al, 1997b).

However, clinical registries are increasingly tapping into existing computerized data repositories to source new cases and to improve the completeness of data collection and follow-up. Therefore it is vital to have patient identifiers that are able to track patients across multiple databases as well as longitudinally. The focus has changed to finding methods for ensuring patient data is held securely and confidentiality is maintained without total anonymisation. For example in Denmark every citizen has a unique identification number, which encodes sex and date of birth (Pedersen et al, 2002). Norwegian cancer registries also use a national personal identification number which makes record linkage easier, less resource intensive and avoids duplicate registrations (Harvie et al, 1996). In the DARTS database, cases are identified by a unique identifying number, called the 'community health number', which is allocated to every patient who is registered with a GP in Scotland (Morris et al, 1997).

Databases also need to collect patient identifiers such as age, gender and postcode to ensure comparisons of patient outcomes are meaningful and for investigation of the influences of socioeconomic and geographic factors on outcomes (Berrino et al, 1998; Black, 2003b). For instance EUROCARE reports relative survival rates, which requires the patient's age, gender and geographical location to conduct this analysis.

2.3.3 Requirement for patient consent

Under the Data Protection Act 1998 all research involving patients requires the patient to give informed consent. However researchers can apply for exemption to use patient identifiable information for research without consent under section 60 of the Health and Social Care Act 2001. This provision is a temporary measure until anonymisation or consent can be put in place (Goldblatt, 2006). Most patients are willing to allow personal and clinical information from their medical records to be used for research, audit and health surveillance (Willison et al, 2003; McKinney et al, 2005; Barrett et al, 2006; Tate et al, 2006) but the limited evidence available indicates that they prefer to be asked for consent either verbally or in writing (Willison et al, 2003).

2.3.4 Consent process

In practice the process of gaining consent presents major obstacles for some observational studies and clinical registries/databases. McKinney and colleagues (2005) had only partial success at obtaining individual signed consent in seven paediatric intensive care units (PICUs) to share patient identifiable information with an externally located national clinical audit database. Lack of staff resources led to one unit not participating and another not fully implementing the protocol. The overall consent rate was only 43% and ranged from 9% to 84% between units. Consent rates were significantly better for children who were more severely ill on admission and for hospital stays of six days or more. Children aged 12-16 yrs were not consented, probably due to confusion among staff over the separate consent documentation required for these patients. Most patient consents were taken by staff nurses, which makes sense as they have the most prolonged and repeated contact with patients and carers in ICU.

Tu et al (2004) attempted to obtain written consent from consecutive patients admitted to stroke units in order to enrol them in the prospective Registry of the Canadian Stroke Network. The overall consent rate was 39% in Phase 1 which improved to 51% in phase 2, following extra staff training and "easing" of their workload. Again participation rates varied from an average of 72% in the best units to 17% in the worst. The consents were obtained by research co-ordinators rather than ward staff. The main obstacle was access to patients. Access issues included patients dying or having left hospital before being approached for consent or potential participants not being admitted at all. Additionally patient access was deterred due to the logistics involved in arranging interviews at a convenient time for the patient during their hospital stay.

Al-Shabi and colleagues (2005) also had major problems accessing patients for consent to include them in a population based observational research study of intracranial vascular malformations. GPs and hospital consultants refused access to 30% of potential participants. Reasons for refusal were patient deceased, cognitively impaired or anxious about their diagnosis. In some cases the doctor did not respond to the request or did not give a reason for refusal.

Similarly Busby et al (2005) found that consent rates varied enormously between eight European congenital anomaly clinical registries that used opt-in informed consent procedures. One registry had 18% missing cases and another estimated a 4% consent rate in the year after implementation of the opt-in consent scheme. Another registry, which requested consent by post, estimated between 15-20% loss of cases due to non response and another was not fully operational due to low notification levels caused by the requirement for consent. Patient refusal was reported as less than 1% by all these registries. However, this group of registries also reported difficulty in persuading busy clinicians to take on the extra workload of gaining consent. In contrast the three other congenital anomaly registries surveyed did not appear to have any problems with gaining patient consent. In one registry consent was obtained at maternity booking to enable research staff to examine all newborns for abnormalities after birth; they reported only two refusals since 1990. Another was a voluntary association of clinicians which obtained verbal consent for registration of data from parents. The third registry used information from interviews conducted with parents, of children with congenital anomalies (and controls), shortly after birth.

2.3.5 Consent bias in population health surveys

If patients are excluded because they have not consented selection bias may be introduced into the analysis and outcomes observed in observational research (Tu et al, 2004 Al Shahi et al, 2005; Tate et al, 2006). Most of the existing literature on consent bias has focused on large health surveys that involve data collection either by post or by interview with the participant.

In a national cohort study 92% of mothers gave consent for linkage of their child's health records with survey data (Tate et al, 2006). However the group that did not consent differed from those that consented in socioeconomic, educational, ethnicity and country of residence. Tate et al suggest that these sources of non-consent bias should be taken into account when analysing linked data from socially and ethnically mixed populations. Dunn et al (2004) analyzed consent patterns from seven UK general practice population surveys. They found that consent by patients to follow-up and GP medical records review were similar with males, younger people (under 50 yrs) and patients reporting the symptom under investigation being more likely to give consent. Consequently these groups may be

overrepresented in these types of studies. A similar study conducted by Woolf et al (2000) of family practitioners, in the USA, yielded some similar evidence but also dissimilar findings. They reported that older age, males and lower functional status were significant predictors of consent.

2.3.6 Consent bias in clinical cohort studies and disease registries

Non participation in clinical registries appears to alter the case mix of patients studied compared to the true patient population. Al-Shahi et al (2005) conducted a prospective follow-up study of a Scottish cohort of adults diagnosed with intracranial vascular malformation on or after 1 January 1999. When a newly diagnosed patient was notified to the study, the team endeavoured to gain patient consent for participation in the study via their GP or hospital consultant. The authors did not find any statistically significant differences between those who consented or not in terms of demographics (age, gender) and socioeconomic status but patients who gave consent to participate had a different and less severe disease profile to non-consenters at first presentation (with the illness). Consenters were significantly more likely to be alive and independent at presentation. These factors significantly changed the results in some important clinical outcomes measured. For example analysis of the whole cohort suggested that presentation with an intracranial haemorrhage conferred a higher risk of subsequent haemorrhage but this association disappeared when the analysis was restricted to consenters only. This prognostic variable, which partially influences treatment decisions, came up with different inferences depending on how the cohort was analysed. Some of the differences observed between non consenters and consenters were due to exclusion from the cohort of deceased patients. In England, , it is possible to include deceased patients in medical observational research without their consent (General Medical Council, 2004a,b). Including deceased patients, in this study, would have reduced selection bias and strengthened the methodological rigor in this instance.

As a consequence of the low and variable consent rate the patients in a study by Tu et al (2004) were not representative of the typical patient with stroke at centres included in the study. In general those who participated were younger, more likely to be alert at admission and more likely to be alive at discharge and their preferred language was more likely to be English or French. Again, excluding patients who died skewed the data significantly as the

in-hospital mortality rate was much lower among patients who enrolled than those who were not enrolled (6.9% vs 21.7%). Selection bias persisted in hospitals with high participation rates and well as those with low participation rates. Tu et al (2004) reported that the data was similar to that collected by clinical trials. For example certain observational inferences could be made about risk factors and outcomes but they were uncertain about the generalisability of the results to the general population with stroke. The data was of limited use for monitoring and planning health care delivery.

In contrast more severely ill ICU patients would be over represented and teenagers underrepresented in the clinical database study by McKinney et al (2005), due to the consent process. The authors suggest that even the 16% level of incompleteness from the best performing unit was too high and it would compromise the database's ability to act as an instrument for monitoring care effectiveness and clinical governance.

2.4 Validation of clinical databases/ registries

2.4.1 Origins of registry data

Clinical registries and databases are frequently populated with secondary data from medical records. Medical record review refers to any study that uses pre-recorded, patient-focused data as the primary source of information to answer the research question (Worster and Haines, 2004). Clinical registries generally use a multiplicity of information sources to populate the patient record including patient notes, clinical and administrative databases, diagnostic test reports, GP records, and Accident and Emergency notes.

The traditional method is for patient information to be abstracted from the patient records by hand and entered into the registry (e.g. the UK Cystic Fibrosis Registry). Modern and well funded registries often use computer linkage as the main system for data abstraction (DARTS database) or a combination of both methods such as employed by the UK cancer registries. Main sources of information for cancer registries are pathology databases and the NHS Patient Administration System (PAS). The hospital PAS records all patient discharges in electronic format using the World Health Organisation (WHO) International Classification of Diseases diagnostic codes (ICD).

2.4.2 Validation of registry data –definitions and scope

Information in medical records is recorded at the point of care and for the purpose of patient care not research, audit or health surveillance. There is generally no protocol or systematic process for giving care or recording the process therefore the information is recorded in a casual manner by multiple providers and observers (Lowenstein, 2005). As a consequence of using these secondary data sources registries are faced with three potential problems which threaten the quality of their data irrespective of the methods used for abstraction. Firstly is the information valid for abstraction i.e. is the medical record a valid description of the patient episode of care? Secondly is the data abstraction process reliable? Finally is the register complete? The following sections will explore the problems with accuracy and completeness of registry data, how these issues can be addressed and their effect on the utility of database information.

2.4.3 Reliability of data abstraction

Data accuracy can be assessed by measuring the reliability or reproducibility of the data (internal validity). Studies identified for this review either measured the reliability of the medical record extraction process prospectively as part of the methodological rigor of conducting the study (Eder et al, 2005) or to ascertain, in retrospect, the reliability of registry data derived from medical records (Every et al, 1999; Fine et al, 2003; Strobl et al 2003). Findings clarify the factors and types of data elements that influence the level of reliability achievable, the instruments and procedures that improve reliability and the impact of data reliability on the utility of a database.

Reliability of data abstracted from medical notes is affected by the type of information abstracted (Eder et al, 2005). These authors reported that if variables were specific and objective in nature such as demographics, documentation of procedures and results, they were abstracted with a high degree of reliability. However clinical data elements that were open to subjective descriptions by clinicians and patients were found to have lower inter-rater agreements between abstractors. For example the patient self-report of symptoms and the variety of terminology used by clinicians to describe clinical examination findings made it difficult for the abstractors to decipher and record these findings. Secondly the clinician's diagnosis/ suspicion of cancer proved difficult to determine from the

documentation. A major source of inter-rater variance was the inconsistency in information obtained from more than one source within the record. Also there was inconsistency in where relevant data was documented because it was recorded by a variety of personnel during different patient visits, sometimes while the patient attended for a separate health problem.

Assignment of a 'final outcome' was the most problematic data item because this required the abstractors to make a subjective decision about whether the patient care pathway followed recommended guidelines. This variable was susceptible to information bias because inter-rater variance was sometimes linked to over interpretation of information actually recorded. This judgement should have been based entirely on the information in the medical record but the abstractors were experienced clinical staff and they found it difficult not to substitute their own clinical assumptions when confronted with missing or inaccurate data.

These researchers imposed a continual cycle of quality improvements which resulted in sustained high-quality information retrieval methods among multiple data abstractors over multiple sites (Eder et al, 2005). For instance an information-priority algorithm was created which listed the hierarchy of data sources that should be used for abstracting data elements. The researchers also developed a glossary that contained terms that were to be considered equivalent definitions of a single variable (examination outcome) from the qualitative descriptions found in the notes to describe clinical findings. This helped promote consistency in data coding of qualitative terms and provided standardisation to the medical record abstraction process. Arts et al (2003) also reported a significant improvement in overall accuracy of data abstraction following clinician training in data definitions and data extraction guidelines.

2.4.3.1 Internal validity examples

Every et al (1999) compared the internal validity of two large US clinical databases – the National Registry of Myocardial Infarction Two (NRMI 2) and the Cooperative Cardiovascular Project (CCP), which collect data on Acute Myocardial Infarction (AMI) by retrospective chart abstraction. Process of care variables and medication showed high agreement (kappa values = 0.75-0.97). Some past medical history variables were under

reported in the NRMI 2 database which would under identify co-morbidities if the results were generalized to population level. In addition identification of adverse events that occurred during hospitalization such as stroke and shock showed lower agreement (kappa = 0.57 and 0.63 respectively) while the clinical outcome variable 'reinfarction' had the lowest agreement (kappa 0.21). The authors suggest that these higher levels of disagreement may be due to differences in the definitions of these variables used by each database; clinicians may also use different definitions for these events which could lead to variation in chart documentation. Therefore these outcomes must be viewed with caution.

Similarly Topp and colleagues (1997) reported that the reliability of data elements in the Danish Cerebral Palsy Register varied according to definition and significance of the specific variable. For instance variables with unambiguous definitions such as maternal diabetes, caesarean section and male sex were very reliable. However there was poor agreement between the medical record and registry entries for gestational age due to a systematic error in how the variable was defined. It was measured as one week higher in the registry then calculated from the raw data in the medical records. This occurred because of confusion among clinical staff over the correct measurement method. The registry relied on this information being reported in the discharge letters therefore this systematic error could not be avoided. The significance of the error depended on the accuracy required; if one week variance was allowed then 84% were registered correctly and if two weeks variance was acceptable then 93% were correct.

In general variables involving calculations appear to be problematic (Arts et al, 2003). Arts and colleagues reported that, even after training, variables such as body temperature and mean alveolar-arterial oxygen difference were frequently incorrect. Body temperature was often incorrect because clinicians forgot to add 1^0C if measured from the groin. Incorrect selection of blood gas samples resulted in inaccuracy in all data calculated using this variable. The main cause of this problem was non adherence to data definitions.

Laustsen et al (2004) assessed the reliability of data in the Danish National Vascular Registry by comparing re-abstracted data with the originals sent to the registry. Data forms were re-completed from the patient's medical notes by each site and also by an independent member of the registry board. There was no difference in reproducibility between the three data sets for data on type of operation and indication for surgery/

diagnosis. Reproducibility of coding for complications and risk factors was poorer and varied considerably between sites. For example in one department it was the primary data set that was poorly coded and in another department it was the re-coded data set that was substandard. Lack of improvement in reproducibility between the data sets from refilled forms and the independent observer was thought to result from weakness in the classification of the parameters under study.

Kantonen et al (1997b) assessed the reliability of vascular surgery cases in the Finnvasc registry by requesting the surgeon responsible for data collection in each centre to resubmit the registry data for a sample of patients. Intra-rater reliability was measured by comparing the refilled forms with the corresponding primary data in the registry. An overall agreement rate of 93% was achieved, similar to that achieved by a previous study undertaken 13 years earlier. However, only 38% of all forms had no differences. The variables differing most were risk factors, with 15% differences, and operation code (10% differences). The problem with the operation codes were thought to be due to the surgeons' lack of familiarity with these codes as they were developed for administrative systems and clinical staff would not use them routinely.

In the follow-up registry form the surgeon states whether the treatment had resulted in an improvement or not. Kantonen et al (1997b) suggest that this could result in biased data as the objective measures used by the surgeons to assess outcome could be misleading and they were not available for all types of vascular surgery. Also follow-up was undertaken at one month which was too short a period to judge the success of some procedures. The authors recommended extending follow-up to one year to improve the evaluation of success/ failure rate. Linkage of the registry for national vital statistics was proposed for improved appraisal of long-term survival analysis.

Pedersen et al (2004) found that the reliability of the data in the Danish Hip Arthroplasty Registry (DHR) was dependent on the type of variable and the ability of the data collection form to capture relevant and complete data. The overall positive predictive value (PPV) of registered diagnoses was 85% but the PPV varied between the different diagnoses. For example a low PPV (30%) was found for fresh fracture of the proximal femur due to confusion over the distinction of this diagnosis with another diagnosis. The authors

suggested this occurred because various definitions exist in clinical practice for this diagnosis, leading to diagnostic misclassification.

The follow-up form did not correctly identify patients with and without postoperative complications. Post operative complications registered were confirmed in only two-thirds of the patients reviewed and specificity of postoperative complications was only 0.3. In addition, a variety of postoperative complications were identified in the medical records that were not registered with the DHR.

Strobl et al (2003) assessed the accuracy of data entered into the Epidemiologic Registry of Cystic Fibrosis against original data in the medical record. The rate of disagreement between the database and medical record was generally low (range 0.4% - 3.7%) due to the routine automatic data checking procedures carried out on the database. Similar to other study results demographic data, test results and treatment data were very reliable. However variables used to measure outcomes were problematic. For example episodes of pulmonary exacerbation were difficult to identify and also verify as there was poor congruence between the different sources of information on exacerbations. Interviews revealed that sites were not consistent in how they interpreted some data recording rules. This was particularly relevant for lung function test, an important outcome measure. There was inconsistency between sites as to whether a good or poor lung function test result was selected for reporting to the registry, which could cause systematic differences between centres.

An independent assessment of the UK National Adult Cardiac Surgical Database, by Fine et al (2003), found that the essential variables required to adjust for case mix were not reliable. Sampling of the registry data against re-abstracted data from medical notes found that mean reliability of all the centres studied was good (k= 0.67) but for each individual centre the average reliability score was only moderate, at 0.44. After a five month intervention of monitoring, validation and feedback to centres a prospective re-sampling of the database showed only slight improvement in reliability (0.53 vs 0.44). The variables targeted for validation were required to assign a preoperative severity (risk) score using the Parsonnet score and the EuroSCORE (European System for Cardiac Operative Risk Evaluation). The Parsonnet risk scores and EuroSCORE calculated from the original and re-abstracted data did not differ significantly. The authors did not discuss if the minimal

improvement in scores occurred because there was little change in data reliability. However, it is generally recommended that researchers strive for a minimum level of interobserver agreement of 60% beyond chance, a kappa value of 0.6 or greater (Worster and Haines, 2004).

A small but significant difference in the Parsonnet risk score recalculated from the original data compared with the score the centres submitted was observed. After the intervention, to improve data quality, the submitted scores were more reliable in the prospective phase. However the reliability of the calculated EuroSCORE remained unchanged throughout because coding of some of the data elements required for this calculation remained problematic. Similarly Arts et al (2003) found no improvement in clinicians' accuracy in calculating APACHE 11 (Acute Physiology and Chronic Health Evaluation) severity of illness scores after training. This was attributed to unreliability and incompleteness in the variables used for the calculations, even after training.

2.4.3.2 Quality of data in cancer registries

Brewster et al (2002) found that the overall quality of cancer registration data in the Scottish Cancer Registry was high. For instance reliability was generally high for demographic, diagnostic and fact of treatment data. However discrepancies in grade of differentiation, staging variables and oestrogen receptor status ranged from 1.5% to 20% between the registry and the re-abstracted data. This made the database less reliable for more specific information needed to assess case-mix. Major inaccuracies in cancer grade and staging is a frequently reported problem for cancer registries and is due to this information being poorly documented and/or missing in medical notes (Schouten et al, 1997; Berrino et al, 1998; Silcocks et al,1999). Schouten et al (1997) reported that many of the disagreements in staging cancer were caused by missing and inconclusive information or from discovering additional investigative results from another source. Brewster et al (2002) recommended collecting the data prospectively on structured proformas in the context of clinical audit, because accurate recording of this information is essential for clinical care.

Phekoo et al (2002) compared a specialist haematological malignancy database against data from the same area covered by the Thames Cancer Registry (ThCR). Discordant

diagnoses were recorded in 20% of the cases that were common to both databases. This was due to certain disease types being misclassified by the Thames Cancer Registry and some rare disorders being underreported. This seemed to be partially due to problems with assigning the correct ICD code for the disease. It was thought that the revised ICD codes for oncology (ICD-O) would enable more accurate and specific diagnosis as it had more refined coding for haematological malignancies.

In addition haematological malignancies are complex to identify and a lack of diagnostic information/ investigations led to some cases being assigned an 'unspecific diagnostic code' or being completely missed. Diagnosis involves several investigations which are difficult to collate as they are performed in different locations and may not be recorded in the hospital's pathology system. Also some diagnoses may be made by clinicians without undertaking all the relevant tests such as histopathology (Phekoo et al, 2002; Berrino, 2003). Following the study a partnership was formed between both haematological malignancy registers. It was thought that actively involving the haematologists (the disease specialists) in collecting and validating data should enhance case ascertainment and diagnostic accuracy.

Middleton and colleagues (2000) examined the accuracy of cancer registrations from an un-corroborated subset of hospital Patient Administration System data in the Northern Ireland Cancer Registry (NICR). This data received a validation check against patients' medical records. Demographic data accuracy was high. However diagnostic data was less accurate and resulted in 19% of the PAS only notifications being excluded from the registry, which amounted to 7.5% of the total cases in the database. Errors included 7.4% of patients incorrectly coded as being diagnosed with cancer and a further 4% had tumour behaviour incorrectly coded as fully malignant instead of benign, in-situ or uncertain behaviour. This error could be partially explained by the fact that these patients had been investigated for 'suspected' cancer. Almost a third had some inaccuracy in coding tumour site. For instance about 27% of cases had a completely different system or organ recorded as tumour site in the case notes compared to that entered into PAS. Common errors occurred for sites that were anatomically close. Also the majority of cases that had been assigned a non specific cancer site in PAS were recoded to a specific cancer site following the notes review. In addition about 17% were prevalent cases.

Most of the errors were false positives therefore the effect of all errors would have been to inflate the overall incidence figures. Sub analysis of the incidence rates would have produced grossly inaccurate figures for some forms of tumour, such as cervical, which would have been inflated by almost 50%. This would have impacted adversely on the quality assurance assessment of the cervical screening program.

2.4.3.3. Improving quality of cancer registries

Middleton et al (2000) suggest that many of the errors in the PAS data, used to populate the NICR, could be reduced with better training for clinical coders and improving the quality of clinical information recorded by clinicians in medical notes. They concurred that PAS data is a valuable source of case identification but there would be an on-going need to undertake a target medical notes review of all uncorroborated PAS data supplied to the registry. According to Middleton and colleagues (2000) the best long-term solution is the development of clinical information systems in routine patient care with mandatory high quality data.

Harvie and colleagues (1996) reported that the data in the Norwegian prostate cancer registry was very reliable. Six percent of the patients' records sampled had one error per record. There were no errors in recording of demographic data. The majority of the errors were in coding of metastases and the 'basis of diagnosis' because several sources of data had to be reviewed to decide the correct code. The excellent reliability of the data was attributed to the high number of cases confirmed by histology (over 95%) and the multiple sources of information received on each case for consistency checks (average number of reports per patient was more than three). In addition, all coding was undertaken at the central registry by trained coders. The authors purport that these measures ensure a high level of internal validity and prevents bias.

In Norway the organizational structure and legal obligations appear to ensure that cancer registry data is reliable and complete. Reporting of cancer cases to the registry is compulsory and since 1983 Norwegian registries have an explicit legal obligation to assess the quality of their own registrations.

2.4.4. Timing of data - is it important?

Brewster et al (2002) found a 24.3% inconsistency in recording of diagnostic date but, in most cases, the re-abstracted incidence date was within six weeks of the registered date. Therefore this level of imprecision in diagnostic date would have minimal effect on incidence information.

Accurate timing of outcome events is important in longitudinal data collection because without timing of data it may be difficult to distinguish between discrete episodes (Strobl et al, 2003). Due to imprecision in recorded medical information these researchers found it difficult to quantify the number of discrete pulmonary exacerbations events the patient experienced. This was due to the fact that fields from different files had to be cross-referenced and assumptions made about realistic time gaps between distinct episodes.

Some authors have reported a problem with data collectors and clinical staff selecting values of physiology variables, such as blood pressure, from outside the specified time frame (Chen et al, 1999; Arts et al, 2003). This led to poor data reliability and inaccurate calculations of severity of illness scores and probability of death predictions. These errors were caused by lack of staff training and non adherence to data definitions and data abstraction rules (Chen et al, 1999; Arts et al, 2003).

In the quality assurance study by Brewster et al (2002) the date of first treatment for each modality was unreliable with between 15 to 25% disagreement between the registry and re-abstracted data. These discrepancies happened because different information was available to the person making the original registration than to the person re-abstracting the data at a later date. Silcocks et al (1999) also reported this problem where relevant patient information becomes available after the case has been submitted to the registry.

2.4.5. Completeness in clinical databases and registries

Completeness is measured in terms of exhaustiveness of case ascertainment, completeness of coverage of the geographical area covered by the clinical database/ registry and completeness of variables collected (Black and Payne, 2003). Completeness of registration or case ascertainment is defined as the extent to which all the incident cases (cancers)

occurring in a target population are included in the registry's database (Parkin et al (1994) cited in Lang et al, 2003).

The research reviewed shows how to assess the completeness of a database, identify the critical issues in bolstering completeness and discusses the consequences of incompleteness on the validity of results derived from the data in the database.

2.4.6 Completeness of follow-up

The independent assessment of the UK National Adult Cardiac Surgical Database (UKNACSD) found deficiencies in completeness of variables as well as deficiencies in reliability. The significant difference between the completeness of data entered into the database and data available in the patients' medical records (25% vs 1%), was largely because of failure to transfer information from patients' notes into the database (Fine et al, 2003). Following the validation check, database re-sampling showed that the proportion of missing data elements fell to 9 % but this was still significantly more than the 4% missing in the patient notes.

2.4.6.1 Accurate survival rates require accurate staged diagnostic data

A UK regional cancer registry investigated by Silcocks and colleagues (1999) could only report crude survival rates as an outcome because the database did not have information on case-mix at diagnosis. The registry relied on information extracted from the hospitals' PAS. This data was extracted by clinical coders from discharge summaries or medical notes. Variables necessary to assess case-mix, such as tumour stage at diagnosis, were invariably not present in the medical notes therefore it was missing from the database. However trained non medical registry personnel were able to reliably impute the stage from the clinical information provided. This validated data then provided very good outcome data for age and stage adjusted survival rates. According to the investigators it was more costly to use trained registry staff to abstract the staged diagnostic data than it would be for clinicians to provide adequate data in the notes in the first place. The most efficient process was for clinicians to formally stage the tumour at diagnosis, in a standardized format, and record it in an accessible part of the notes or in a clinical database.

2.4.6.2 Incomplete treatment data due to time lag

Silcocks et al (1999) reported that treatment data was incomplete in the cancer registry as it was based on the information available at the time of original coding and also on the ability of the coders to extract the relevant information from what was available in the notes. Silcocks and colleagues (1999) suggest that treatment information will be incomplete if it is submitted to the registry following the patients' initial discharge from hospital. In practice there is often a large time lag between when the patient is first diagnosed by the clinician and when diagnostic tests are performed to verify diagnosis prior to commencing therapy. Treatment data will not be captured by the registry if the patient starts it as an outpatient because this information is not recorded on PAS.

Du and colleagues (2006) reported the same problem with incomplete follow-up treatment data in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) breast cancer registry. Incompleteness of chemotherapy and hormone therapy information was thought to arise because patients were not followed up for long enough after diagnosis to capture this data. Chemotherapy is started after surgery and hormone treatment may be started later. Secondly these treatments may be commenced in places where the registry do not collect data such as outpatient clinics or in the physician's office. Also if patients received treatment in external states then this information may be missed altogether or severely delayed in being recorded in the registry. The authors suggest that underreporting of chemotherapy and hormone therapy use in breast cancer should be noted when using SEER data. Similarly Kantonen et al (1997b) deemed follow-up information difficult to collect for vascular surgery as some patients did not attend their follow-up appointments or their care was transferred elsewhere. This problem resulted in 30 day follow-up information missing for 18% of cases in the Finnish Vascular (Finnvasc) registry. Du et al (2006) conclude that it would be better to combine patient data from different sources to obtain more complete information.

2.4.6.3 Under reporting and outcome variables

Strobl et al (2003) reported that some outcome variables were under-reported in the cystic fibrosis registry. Hospital admissions were significantly under-reported by one centre, which would have caused systematic bias in the results. Similar to the findings of other studies recording of death data was incomplete, with deaths being under reported by 8%. In

addition 21 causes of death and 17 dates of deaths were missing from the database. The dates of deaths were entered as discontinuation dates in the registry. Strobl et al (2003) suggest that incomplete outcome data is problematic for economic evaluations. Neither resource use nor health outcomes can be estimated reliably without knowledge of the extent of under reporting. Variations in clinical practices between centres, such as local treatment protocols and shared care arrangements with local-non specialist clinicians, were not well recorded by the registry. The authors suggest that this risks misattributing variations in outcome to recorded variables when they may arise from unrecorded variables.

Fine et al (2003) found that the number of total deaths originally submitted to the UKNACSD was under reported in some centres and these errors alter mortality calculations substantially due to the small numbers of total deaths. 'In hospital mortality' rate was the only outcome indicator measured therefore this would have a substantial effect on all results. Mortality records were uniformly poor in all centres studied and there were problems with computer software, particularly in transferring patient data between different software systems. In the future all deaths were going to be tracked via the ONS, which should improve completeness.

2.4.6.4 Risk factors under reported

Topp et al (1997) found that two risk factors were significantly underreported in the cerebral palsy registry. For example placenta abruption, an important predictor of risk, was underreported (sensitivity = 42%), possibly because this is a clinical diagnosis without clear cut criteria. Completeness of this variable would have been improved if obstetric discharge letters were sent to the registry.

2.4.6.5 Missing data bias

Missing values are usually managed by case deletion but if missing cases are not random then the impact of exclusion will be non random which may produce biases in any analyses (Norris et al, 2000; Worster and Haines, 2004). Case deletion also reduces the sample size therefore even if missing data is random it may impact on the utility of the database. For example investigators may not have enough information to adjust for case mix or to report outcomes reliably. The second method of managing missing data is to impute the result,

typically by assuming the absence of the variable if the field is left blank or, thirdly, find alternative data sources to improve completeness (Norris et al, 2000).

These investigators compared the impact of these three methods for managing missing variables needed for risk adjustment in a cardiac surgery clinical registry. The data were missing in non random patterns with a higher level missing in one site, more data missing earlier in the year under study then later and variables were often missing in clusters. The database with improved completeness preformed best for predicting risk and the database which excluded cases with missing variables was second best. They found that imputing a negative or zero value for missing predictor variables underestimated the true prevalence of risk factors. However, the database with improved completeness was only marginally better than the other two models. The authors suggest that the extra cost involved in improving completeness was worthwhile as the enhanced database had clinical face validity and the results were more generalisable because one quarter of the patients would have been excluded if cases with missing variables were deleted.

2.4.7. Completeness of case ascertainment

In the comparison study conducted by Phekoo et al (2002) only 28% of incidence cases were recorded in both databases, 42% were recorded only in the Thames Cancer Registry (ThCR) and 30% were recorded only in the haematology malignancy database. The Thames Cancer Registry obtained records on haematological malignancies from 30 different specialities and haematology accounted for 35% of these cases. This illustrates how difficult it is for a specialist database to achieve completeness as the haematologists were only submitting data on their own patients and therefore patients treated by other types of clinical specialists were missed. Even the ThCR was only 70% complete and of these 31% were identified through death certificate only (DCO).

The high level of DCOs is a strong indicator that case ascertainment is very incomplete and case identification methods inadequate (Berrino et al 1998; Berrino, 2003). This suggests a bias in survival estimates but does not indicate the direction of the bias. For example missing cases, in a cancer registry, will include patients who do not die, for instance patients who are cured and cancer will not appear on the death certificate (Capocaccia et al, 2003). This has the effect of underestimating survival rates. Omitting

DCO cases may introduce a selection bias if cases are systematically different to registered cases. For instance DCO cases may be very ill patients with short survival and exclusion of these cases tend to overestimate survival rates (Scotter et al, 2000; Capocaccia et al, 2003).

DCO cases cannot be included in survival data unless a date of diagnosis is found therefore some registries, including English regional cancer registries, track back DCOs to find a diagnosis date so patients can be included. This increases the completeness rate but causes selection bias and can result in underestimates of survival due to the non random case ascertainment of lethal cases (Berrino, 2003). This bias may affect survival estimates of registries with a high proportion of DCOs to start with but only a small proportion remaining after the track back exercise (Stotter et al, 2000; Phekoo et al, 2002; Berrino, 2003).

 In a similar study Stotter et al (2000) reconciled incident breast cancer cases in the Trent Cancer Registry (TCR) with Glenfield Hospital's breast cancer clinical database. This process improved the completeness of the registry by 12% and changed the characteristics of patients registered. The missed cases were not typical of the cohort as a whole but consisted of a subset of older women with a shorter life expectancy. In addition 25 (of 62) cases identified through DCO in the TCR, had a diagnosis date identified in the Glenfield database; these patients had a median survival of only 11 months. None of the patients who received private health care were in the TCR.

The improved case ascertainment had the effect of increasing breast cancer incidence rates and the five year survival rate decreased from 62% to 59%. Older women were systematically underrepresented in the registry because the main source of registration was through the hospitals' Patient Administration System. Therefore patients managed as outpatients only, without surgical intervention, were likely to be omitted. The median age for those who underwent surgery was 56yrs compared with 77 for those without surgical intervention; consequently older women were systematically omitted. Similar to Phekoo et al (2002) amalgamating the two sources of information improved both the rate and representativeness of breast cancer cases registered thus increasing the credibility of any outcome information derived from the data.

Another British study by Pobereskin (2001) examined the completeness of brain tumour registration in a Regional Cancer Intelligence Unit with a clinical database called the Devon and Cornwall database (DCDB). The DCDB was taken as the gold standard because it was developed as part of the Devon and Cornwall brain tumour incidence study which had exhaustive methods of case ascertainment (Pobereskin and Chadduck, 2001; quoted in Pobereskin, 2001). Only 52% of cases ascertained in the DCDB appeared in the registry and certain tumours were systematically under reported such as benign tumours in younger patients, without surgery. Under ascertainment of cases occurred because most notifications to the regional cancer registry were through the hospital PAS, which would be likely to only identify patients with surgical interventions. Again there was no mechanism for registering patients if they were treated through the outpatient department. However only 64% of patients admitted to hospital for operation were notified to the registry via PAS and no explanation was given why so many inpatients were missed by this system.

Incidence data from this registry would be particularly unreliable as incidence rates would be underestimated and survival rates overly pessimistic as younger people with better prognosis were undercounted.

Stefoski Mikeljevic et al (2003) evaluated the completeness of skin cancer registrations in the Northern and Yorkshire Cancer Registry and Information Services (NYCRIS) during 1994. The proportion of under ascertainment of malignant melanoma (MM) was 12% and non-melanoma skin cancer (NMSC) was 17%. The effect of including the additional missing cases increased the regional estimated incidence rate, for that period, from 7.5 per 100 000 per annum to 8.4-9.3 for MM.

2.4.7.1 Completeness of reporting and pathology data

Furthermore, completeness of reporting rates to the NYCRIS varied considerably between pathology laboratories (from 32% to 98%). A likely cause was the absence of quality control mechanisms in any of the laboratories to ensure skin cancer cases were notified to the registry. Investigation of the PAS data showed that it was not sufficiently complete or reliable to act as a primary notification source because there was considerable variation between hospitals in the quality of information extracted, especially with respect to under

reporting of skin cancers. Only half of cases identified from GP practices were in the registry.

The primary routine means of notification of new cases to NYCRIS were pathology laboratory reports and this was supplemented by data from PAS. PAS and the pathology information together increased the matching rate in comparison to either source alone. For example 95% of all patients identified through pathology laboratories and PAS had a matching record in the registry compared to 80% if identified by either source alone. According to Stefoski Mikeljevic and colleagues (2003) the most effective strategy to enhance case registration would be the routine linkage with PAS information supplementary to that from pathology laboratories. The authors suggested that it would not be cost effective or efficient to link to GP computer systems as a source of case identification because GP practices only accounted for a small proportion of total cases and each GP practice only had a few cases per year. It was recommended that clinicians and GPs send biopsies for histopathology verification on all suspected skin cancer patients. This would improve case ascertainment as well as being considered good clinical care.

Brewster et al (1996) reported that ascertainment of cases by the Scottish cancer registry was very efficient for most sites with an overall completeness rate of 94%. Missed cases were not equally distributed and some cancers (e.g. non-melanoma skin cancer) had a higher percentage of cases not registered. Estimates of completeness were also lower for some rarer cancers. The effect of missing cases is more dramatic on estimates of incidence where small numbers are involved; therefore data from pathology databases would be very beneficial for identifying rarer cancers. However using the 'pathology only' to identify cases would have led to a large proportion of false positives because 36 percent of 'missed cases' identified by this source were ineligible for registration. Overall computerised pathology databases were seen as a useful additional source for case ascertainment but needed to be collaborated with additional sources of patient information.

2.4.7.2 Scandinavian databases and completeness rate

Harvie et al (1996) reported the deficiency of reporting incidence cases of prostate cancer to the Norwegian cancer registry as less than 1%. The high completeness rate was attributed to their system of complementary acquisition of data from three different sources

(hospital departments, histopathological laboratories and National Death Register). However they found that a large number of patients in the registry were not found on hospital lists reflecting incomplete recording of diagnosis in hospitals. Therefore hospital lists or diagnostic indices were not reliable sources of information at that time period. Pedersen et al (2004) reported that the overall completeness of the Danish Hip Arthroplasty Registry (DHR) for registration of primary total hip arthroplasties (THAs) and/or revisions was 94%. There was a lower degree of completeness for revisions than for THAs (81% vs. 94%), for university hospitals than for other hospitals (91% vs. 95%) and for low-volume hospitals (87%) compared to medium (92%) and large volume hospitals (96%).

The authors found that some operations were misclassified as revisions in the reference database (the Danish National Register of Patients (NRP)) but were correctly classified as primary THAs in the DHR, which could explain why there appeared to be a lower level of completeness for revisions. The higher rate of incompleteness of registrations from some of the university hospitals was attributed to the large number of temporary trainee surgeons who might not be informed about the registry by the permanent orthopaedic surgeons. Reporting cases to the registry is compulsory so that might explain why there was such a good overall level of completeness.

Kantonen et al (1997b) reported that the mean percentage of missing cases in the Finnvasc registry were 19% (range 0-47%) and completeness varied considerably between participating centres. Emergency operations and endovascular surgery were the most common missing cases. The authors suggest that centres with low registration may not be registering cases with unfavourable outcomes. Also problematic procedures that occur at night and those undertaken in the angiography suite needed further investigation.

These results showed a lack of improvement in case ascertainment rates from a previous validity study conducted 13 years earlier. Kantonen and colleagues (1997b) suggest that lack of improvement over time may be because some centres are less interested in participating in the registry due to the time consuming task of filling in the forms properly, checking and mailing the data. No monetary compensation was given to centres. The only benefit was the feedback of their centre results and the overall results of the whole country for comparison. Similar to Pedersen et al (2004) some of the hospital databases, used as the

reference database, had missing cases therefore hospital registers should not be the absolute reference. The authors believed that accuracy of hospital records might improve in the future because charging would be based on the surgical procedural code for the patient.

Topp et al (1997) estimated that the completeness of the Cerebral Palsy Register in Denmark was 85% but missing cases had similar characteristics to enrolled cases therefore the under ascertainment did not create selection bias in the data. However, the improved completeness of the register, following the validation study, could introduce a potential bias when estimating prevalence rates over time as any change in rate might be due to the improved completeness rather then a real change in the rate.

The study also found that the reference database used for the validation (the Danish NRP) was systematically missing mild cases because these patients were not hospitalised. Consequently, using this database alone for prevalence estimates would have lead to selection bias in the results. There were also a significant number of false positives in the NRP, which were attributed to non specialist clinical staff mis-diagnosing cases. Topp and colleagues (1997) suggest that cerebral palsy is difficult to diagnose in practice due to vague diagnostic criteria and a possible low diagnostic agreement even between specialist clinicians. They recommend that explicit criteria be used for making the diagnosis and, preferably, the same specialist take responsibility for diagnosing cases.

2.4.8 Timeliness of case ascertainment

In the study by Phekoo et al (2002) only 39% of incident cases were reported to the regional registry during the year of diagnosis, 44% were reported after one year and 17% two to three years later. Harvie et al (1996) also reported that completeness of case ascertainment improved with the number of years following diagnosis from 95% after one year to 99% after five years and after 10 years, registration was near 100%.

Delays in identification of cases and completing relevant follow-up, results in significant time lags in reporting of registry data such that it can be considered out of date when made public (Black, 2003a; Berrino, 2003). The problem is compounded by the additional time required to check, analyse and publish the information (Berrino, 2003). Patient care

changes over time therefore publishing results that relate to the last decade may not be that useful for current clinical management and planning services (Berrino, 2003; Black, 2003a; Richards, 2007). Statistical methods have been developed and registry procedures modified to reduce time delays in reporting cancer survival rates for the EUROCARE studies (Brenner et al, 2002; Berrino, 2003). Even with these measures the last publications related to patients that were diagnosed five to seven years previously; therefore further improvements in timeliness are required (Richards, 2007). The Diabetic Audit and Research in Tayside Scotland database appears to have current data because it is regularly updated with patients by automatic computer linkage to multiple sources for case ascertainment (Morris et al, 1997). Applying some of the principles and practices from this model might help improve timeliness.

2.4.9 Geographical coverage

Coverage per country varies from 100% to less then 10% in the EUROCARE population-based cancer studies (Capocaccia et al, 2003). Countries with low coverage are included in estimating European wide survival rates by using weightings proportional to the reciprocal of the registry's coverage for that country (Berrino et al, 1998).

However study results from registries with low coverage may or may not be representative of the country as a whole so caution is needed if the data is used to compare inter country differences (Berrino et al, 1998; Capocaccia et al, 2003). There is evidence to suggest that countries with low coverage can be representative. For instance four countries in EUROCARE-3 had increased their national coverage substantially from the previous EUROCARE-2 study but the overall cancer survival rankings did not change for any of them (Capocaccia et al, 2003).

However Berrino and colleagues (1998) did find outlier values for some high lethality cancers in countries where the registries had a low proportion of coverage. In this situation survival rate estimates will be subject to large random variability. Also 'case selection' is likely to occur during the early years of a population-wide collection if a registry previously operated as a clinical database/registry (Capocaccia et al, 2003). For example the Munich registry was omitted from aggregate analysis with the other German registries in EUROCARE 3 because the researchers were worried about the representativeness of the

results. This was a new-population based registry which used to be a clinical registry. The authors suggested that the registry required a longer period of incidence data collection and more health state information (disease stage) to determine if the high survival rates observed were real or due to case selection.

Indeed Strobl et al (2003) stated that complete geographical coverage of any geographical region by the Epidemiologic Registry of Cystic Fibrosis was unlikely even in participating centres where registration was complete. This was because specialist centres do not draw patients from clearly demarcated regions and not all patients whose care was shared with local hospitals were registered in the database. Therefore they did not know if their patient sample was representative of the UK cystic fibrosis population.

Every et al (1999) reported higher hospital mortality in the NRMI 2 database due to inclusion of non-insured older patients, which were excluded from the CCP database because it was exclusive to Medicare beneficiaries. The authors did not comment on the impact of this finding but exclusion of this group may cause selection bias in the CCP, for example leading to skewed mortality outcome data.

These examples highlight the importance of knowing the purpose of a database and its methods of case ascertainment in order to assess if reported results are generalisable to the total population or to specific subgroups only.

2.4.10 Indirect quality indicators

A range of routine quality checks can be performed on clinical data repositories to assess their accuracy and completeness (Berrrino et al, 1998; Strobl et al, 2003; Harrison et al, 2004). The EUROCARE studies used indirect indicators, based on cross-validation analysis of consistency of the relevant variables (Berrino et al, 1998). Data queries were sent back to the registries for checking and correction if possible. Records returned after review were rechecked and included for analysis if they passed the quality checks. Records characterised as having 'major' errors were excluded but not deleted from the database in case they were corrected in the future. All changes to data were logged for future reference. Comparable procedures were employed by the NRMI 2 database which proved effective at maintaining reliable and complete data (Every et al, 1999). Arts et al (2003)

also reported a much lower error rate following automatic data checks compared to data that was not subject to this form of checking.

Other indirect quality indicators used by EUROCARE included assessment of the proportion of cases ascertained through death certificate only (DCO), microscopically verified cases and cases lost to follow-up by country (Berrino et al, 1998). In addition unexpectedly high survival for cancers known to have very poor prognosis may indicate inaccurate diagnosis and/or deaths not known to the registry (Berrino et al, 1998).

2.5 Discussion

2.5.1 Registry uses

The strength of clinical registries and databases is that information reflects what is happening in routine clinical practice. They provide rigorous scientific evidence about what is and is not clinically effective. Over recent years their utility has evolved from providing basic information that allowed only descriptive comparisons of levels of activity and crude outcomes. Current registries are capable of achieving much more because they use expanded datasets and sophisticated statistical methods. Their results identify problems and often the source of the problem for further action. Registry information has been used to document the natural history of diseases, map the care pathways for patients and demonstrate if patient care followed recommended guidelines. Accurate prognostic models have been developed for performance monitoring and to enable accurate predictions of outcomes of care and treatments. Health technology databases are ideal for evaluating the medium and long-term effectiveness and safety of treatments where efficacy has been proved by clinical trials (Ferster et al, 2001; Padkin et al, 2001; Strobl et al, 2003). However to assess diffusion and equity the registry should include the entire client group not just the cohort that had the intervention/ treatment (Raftery et al, 2005). In addition utilizing registry data in local clinical settings, such as for individualized patient reports, helps clinical management.

2.5.2 Benefit to patients

The overall objective of better information on services and outcomes is to benefit the patient. The Department of Health wants this information to be the driver for enhanced patient choice, improved service quality and to underpin stronger commissioning (Department of Health, 2007a). Therefore the ultimate test of whether registries lead to health benefit depends on how the information is used to change and improve practice. Registry outputs provide the stimulus and evidence to initiate action and the instrument to monitor progress (Keogh and Kinsman, 2004; Harrison et al, 2006; Department of Health, 2007a). Translating this information into effective action is required if a registry is to ultimately benefit the patient (Keogh and Kinsman, 2004).

However affecting change in clinical practice is complicated and difficult to achieve (Dellinger and Vincent, 2005; Harrison et al, 2006). For example cancer registry information, especially EUROCARE results, have led to government initiatives to improve cancer outcomes, including the NHS Cancer Plan (2000) and the Cancer Reform Strategy (2007). Unfortunately the evidence demonstrated that while cancer outcomes are improving in the UK, relative survival still lagged behind comparable European countries rates (Department of Health, 2007a, Richards, 2007). Therefore cancer care has not improved enough to eliminate the deficiencies identified by the EUROCARE studies and cancer patients in parts of the UK are still receiving sub-optimal cancer care.

In contrast UK adult cardiac surgery outcomes are comparable with outcomes internationally, which is, at least partially, attributed to the success of the UK National Adult Cardiac Surgical Database for its role in national comparative audit and performance monitoring. This database is an integral part of the society for Cardiothoracic Surgery of Great Britain and Ireland (SCTS) (Society of Cardiothoracic Surgery of Great Britain & Ireland, 2008). Now incorporated into the Central Cardiac Audit Database, it is an essential source of data on cardiac surgical outcomes which feeds into their quality improvements programme. This model, where practicing clinicians take ownership and responsibility for improving patient care appears to be more successful then top down interventions by government agencies. An equally important incentive was the exposure created by comparative audit where the performance of individual cardiac surgeons and units were directly compared with other local, national and international services (Keogh et al, 2004).

2.5.3 Determinants of utility

The fundamental requirement for a registry to be valuable is the availability of high quality, usable and relevant information (Department of Health, 2007a). However there appears to be a trade off between quality and depth of data collection. The more variables collected the more questions can be answered with registry information but one has to balance this with the cost and risk to data quality of enlarging the data set (Raftery et al, 2005). For example, in comparative audit the information is often detailed enough to identify both good and poor performance and even isolate risk factors but more detailed patient and institutional information is often needed to tease out the cause of the problem. This is perfectly reasonable as a single method of enquiry is often not sufficient to study complex issues such as healthcare and disease processes (Spiegelhalter, 2002). Conducting targeted smaller studies on a subset of the registry population allows more in-depth data collection and analysis to answer specific questions such as why differences in outcomes occur between countries, units or patient groups (Berrino, 2003).

2.5.4 Registry methodology

Greatest benefit is derived from a registry if the entire patient population for the designed geographical area is included and comprehensive health data is collected at the level of the individual patient. Patient level data should include demographics, diagnostic and treatment variables, health states and outcomes. This will ensure the registry can answer questions on effectiveness, equity and diffusion (Raftery et al, 2005) and be used locally for clinical management and audit (Metha et al 2004). Length of follow-up influences the outcomes that can be measured.

Ensuring the registry is set up and adheres to these principles requires rigorous quality procedures and standards. There are several processes that enhance the quality and efficiency of a database such as electronic linkage and individual patient identifiers. Registries/ databases use observational research methods therefore they are susceptible to the methodological difficulties inherent in this form of research. Major categories that were identified as possible threats to the validity of any analysis undertaken are data validity, reliability, completeness and timeliness. Processes and procedures used for gaining patient consent and for data collection determine how vulnerable the registry is to such

methodological weaknesses. The impact on registry outputs of these methodological deficiencies depend on the scale and type of inaccuracy and/or bias introduced. This in turn can limit how the data is analysed thereby limiting its usefulness. Routine internal validity checks and external validation procedures will help prevent these difficulties. The research reviewed here suggests that current registries are of patchy quality. In an effort to tackle this problem various government policies have been initiated in recent years, with varying degrees of success (Keogh et al, 2004; Department of Health, 2007a; Richards, 2007).

2.5.5 Electronic computer linkage

Electronic linkage with other sources of relevant patient data improves the efficiency and effectiveness of registries. It decreases the burden of data collection, reduces transcription errors, and improves timeliness and reliability by cross validation of data from several sources. Most modern registry models use a combination of manual and electronic data collection methods but with increasing computerization in healthcare the shift is towards fully automated facilities. This functionality is essential in the long-term to enable the registry to attain its maximum potential and should be considered in the design. Therefore introducing automated enhancements on an incremental basis should be considered as a medium to long-term goal for the sickle cell disease registry. However implementing automated registry processes is complicated and expensive therefore this option requires further investigation in terms of feasibility, cost, and IT specialist requirements and equipment.

2.5.6 Record linkage

A national personal identification number (PIN) such as that used in Scotland and the Nordic countries is the most efficient and effective for tracking patient records but these PINs are not completely secure as they encode date of birth and gender. A better option would be to use the NHS number, introduced in England and Wales, which is a secure unique patient identifier. All newborns are now issued with a NHS number and there is a national drive to ensure every UK citizen has an NHS number (NHS Information Authority, 2001; Department of Health, 2007b). However, it is not yet universally used as the principal patient identifier in healthcare facilities, including NHS trusts (Department of Health, 2007b; NHS National Patient Safety Agency, 2008). Therefore, for the foreseeable

future, English registries will continue to require other traditional patient identifiers in conjunction with the NHS number to facilitate lateral and longitudinal linkage of patient records (NHS National Patient Safety Agency, 2008).

2.5.7 Efficiency and effectiveness of consent process

Consent procedures for databases need to be decided on a case by case basis. Problems with the consent process have resulted in very variable consent rates between registries and clinical databases and between different sites within the same registry/database (Verity and Nicoll, 2002; Tu et al, 2004; Al-Shahi et al, 2005; Busby et al, 2005; McKinney et al 2005). Success rates depend on the type of disease and patient under study, logistics of the process, resources involved and the enthusiasm, training and experience of all the personnel involved in gaining consent (Woolf et al, 2000; Tu et al, 2004; Al-Shahi et al, 2005; Busby et al, 2005;McKinney et al 2005). The predictors of consent for clinical registries appear to be the ability to have good access to the patient, pro-longed or repeated contact and the health status of the patient. In addition staff must be motivated, competent, have the time and be supported to ensure high consent rates. Patients with cognitive impairment and where there are language barriers are more challenging. Therefore to be successful registries must monitor consent rates and identify factors that influence whether patients consent or not. Deficiencies in the process can be targeted for improvement though an audit cycle framework.

2.5.8 Deceased patients

Patients that die are less likely to be consented (Tu et al, 2004; Al-Shahi et al, 2005). There is provision, under the English information governance regulations, for researchers to use deceased patients' medical notes for medical research, without consent as long as patient confidentiality is maintained and there is no risk of harm to surviving relatives (General Medical Council, 2004a, b; Singleton and Wadsworth, 2006). The pertinent statutes governing access to the health records of deceased patients are Access to Health Records Act 1990 and section 251 of the National Health Service Act 2006 (The Stationery Office Ltd, 1990, 2006). Increasingly, the Freedom of Information Act 2000 is being used to support requests for access to such records (Bonnici and Choong, 2009). However, this regulatory framework is complicated and gaining access is difficult to achieve (Kalra et al,

2006; Bonnici and Choong, 2009). Researchers may need expert advice on interpretation of the statutes before making a request for data (Kalra et al, 2006; Bonnici and Choong, 2009).

Locating medical notes for patients, are their death, is a major problem as they are often archived off-site or missing (Middleton et al, 2000). Du et al (2006) found that where retrieval was possible is took time and often involved a fee because of offsite storage. In addition the retrieved files were frequently incomplete as they had been thinned. Excluding deceased patients because of incomplete or missing information may cause systematic bias in results if these subjects are not typical of the rest of the cohort.

2.5.9 Effect of non consent

Despite the best efforts not everyone will consent to longitudinal studies or research involving their medical records (Dunn et al, 2004). Therefore it is important to compare the characteristics of patients who consent and those that do not to identify if there are systematic differences between the groups. Selection bias may compromise the validity of some analysis and may alter interpretation of results (Dunn et al, 2004). It may be necessary to assess the impact of bias on outcomes by conducting sensitivity analysis between consenters and the whole cohort. This will not be very fruitful for clinical registries if clinical variables are not available for non consenters. Ensuring large sample sizes to take account of non consenters will reduce the potential effect of bias (Dunn et al, 2004).

2.5.10 Data reliability

The onus is on the abstractor to extract the data reliably and in an unbiased manner from the medical record. Problems arise because of missing data, conflicting or inconclusive information, interpreting the information due to non standardisation of recording, ambiguous definitions of data variables or complexity of the variables being measured. For example clinical data elements that were open to subjective descriptions by clinicians and patients were found to have lower inter-rater and intra-rater agreements. Adverse events which occur in hospital and complications seem to be particularly problematic. This possibly is because of their unpredictable nature where abstractors are not looking for

them. In addition they might occur after the follow-up cut off date or the data collection proforma is not good enough to capture this information reliably. The cancer registry research suggests that mistakes frequently occur where tumour sites are anatomically close, where there is no histological verification and because stage and grade information is missing or inaccurate. Inconclusive information such as 'suspected cancer' or suspected disease progression is invariably coded incorrectly, usually leading to false positives. Mortality data appears to be universally inaccurate due to poor hospital mortality records and registries not having adequate follow-up procedures to identify if a patient has died.

Variances occur in recording if the abstractors are required to make a subjective decision about a variable. This happens if the information in the record is ambiguous or conflicting leaving abstractors with three options: deduce the correct answer, leave it blank or be non committal (e.g. non-specific cancer site). A further problem is introduced if data collectors are required to make a judgement about the outcome of an intervention especially if there is any room for subjectivity. For example Eder et al (2005) found that experienced clinical staff substituted their own assessments where data was lacking. Lack of reliability occurs because these data types are difficult to extract from the medical record and information bias may be introduced when abstractors have to make subjective decisions about the data.

2.5.11 Impact of data reliability on the utility of the database

The impact of imprecision in a data element depends on the significance of the error for analysis, its magnitude and whether it is random or not. Systematic errors can arise if variables are interpreted differently by groups of clinical staff or different registry sites (Topp et al, 1997; Strobl et al, 2003). As the error is not random this can lead to misleading results and the significance of the error depends on its magnitude. For example in the study by Stobl et al (2003) some centres were reporting the poorest lung function results for patients while others were reporting the best. This was an important outcome measure of the intervention under study therefore this would make comparative analysis between centres unreliable. However if the measurement error lies within the parameters permitted for that variable then it will not compromise the results (Topp et al 1997; Brewster et al, 2002).

Bias and unreliability is frequently introduced where abstractors/ clinicians have to make judgement about data and report this as a final score or outcome. The probability of error is reduced where scoring systems or decision making processes are objective so there is less opportunity for personnel to be influenced by their own opinions about the patient or outcome (Eder et al, 2005). However, even objective systems can be unreliable. For example if each site uses a slightly different measurement method, or due to the variance introduced by different staff with variable expertise and training doing the calculations or due to the calculation being inappropriately applied (Kantonen et al, 1997b ; Arts et al, 2003; Fine et al, 2003; Harrison et al, 2004). Furthermore if the variables used for the calculations are unreliable or incomplete then the scores themselves will be inaccurate irrespective of the skill of the person doing the calculations (Chen et al, 1999; Arts et al, 2003; Fine et al, 2003). These errors can effect outcome measurement by over or under estimating benefit depending on the direction of the error and therefore make comparative analysis unreliable.

Inconclusive information about a diagnosis or disease progression often leads to false positives and is common where it is difficult to confirm diagnosis by objective measures such as histology. This can have the effect of inflating incidence rates, which would be misleading in subgroup analysis where numbers are small. If this information is used for evaluation of interventions, such as screening programmes, then it would underestimate beneficial outcomes. However, if it is known with certainty that a systematic error has occurred then it can be accounted for in the analysis or explained in the results.

The degree of accuracy of the data determines how it can be used or the level of analysis achievable. In principle the more accurate the data the fewer limits on its uses. For example minor errors in the last three digits of the patients' address postcode could prove problematic if postcode was relied upon for linking patient data to other sources or for subgroup analysis at the postcode sector level (Middleton et al, 2000; Brewster et al, 2002). In the UK Cardiac Surgical Database the degree to which the data can be stratified depends on its reliability (Spiegelhalter, 2002; Keogh et al, 2004). If the objective of this database is to facilitate patient choice about cardiac surgery then the public and clinicians require detailed risk adjusted tables of outcomes published in a comparative fashion (Fine et al, 2003; Keogh et al, 2004). This task necessitates reliable information on well defined prognostic factors such as severity and co-morbidity for case mix adjustment so that fair

comparisons between surgeons and units can be undertaken (Keogh et al, 1998; Fine et al, 2003). However if the objective is to show that a surgeon is safe for quality assurance purposes then the data demands are slightly different. The method used by the UK Cardiac Surgical Database was to agree a threshold level for the outcome of interest (i.e. unacceptable mortality) and then show where each individual surgeon's results lay relative to that threshold. The database initially presented its results in this format because variables needed for full risk adjustment were unreliable and incomplete (Fine et al, 2003). This level of information was sufficient to identify outliers for further investigation (Keogh et al, 2004) and proved sufficient to show (in retrospect) that Bristol Royal Infirmary had excess mortality for paediatric open heart surgery during 1991-1995 (Spiegelhalter, 2002).

This is similar to the problems encountered by the UK cancer registers and EUROCARE. Inaccuracies in case mix can cause important biases in survival data. For example where there is a different case mix of tumours with a different prognosis in the same ICD category (Berrino et al, 1998). These deficiencies do not prevent analysis and publication of data from cancer registries but it can limit the level of analysis undertaken. For example cancer registries usually only undertake basic analysis to identify and report differences (and the scale of differences) in relative cancer survival between groups and geographical regions (Berrino, 2003). In the case of the EUROCARE project, outlier data are investigated by further in depth analysis which involves smaller studies where extra clinical and pathological information is collected on random samples of patients.

2.5.12 Processes to improve data reliability

This review highlights the need for robust data collection forms to capture all essential data with clear evidence based definitions of all data elements for use by all data collectors. Furthermore it is critical that different databases on the same topic share the same dataset, definitions and data collection methods to ensure comparability of results and amalgamation of data if required (Berrino et al, 1998; Magnani et al, 2001; Arts et al, 2003). Checking multiple sources of information for consistency in clinical variables improves reliability of individual patient data (Harvie et al, 1996). Factors which increase accuracy include adequate staff training, standard rules for the data abstraction process and for reporting of variables, familiarity with the coding system and ease of data completion (Berrino et al, 1998; Chen et al, 1999; Arts et al, 2003; Harrison et al, 2004; Eder et al,

2005). Linking registries to national vital statistics is the best method of insuring accurate mortality information for both short and long-term survival analysis. A good example is the UK regional cancer registries which have a uniform process for registering every new case of cancer diagnosed in the registry's population and a standard dataset on each registration is submitted to the Office of National Statistics (Department of Health, 2007a).

However, regular monitoring systems are needed to ensure staff adherence to registry protocols especially data definitions and data abstraction rules (Chen et al, 1999; Arts et al, 2003; Fine et al, 2003). Other measures which have improved data quality include imposing a legal obligation on registries to produce high quality information and linking hospital reimbursement to activity data so there is an incentive to code patient activity accurately (Harvie et al, 1996; Kantonen et al, 1997b).

2.5.13 Coding principles

Coding for disease must be comprehensive and 'exclusive' so that each data element can be captured accurately (Stein et al, 2000; Young et al, 2001). To be able to develop a reliable coding system there has to be agreed definitions for all variables, especially difficult data elements such as some diagnoses (Chen et al, 1999; Keogh and Kinsman, 2004). Coding aids can be developed to assist classification and coding of qualitative terms (Eder et al, 2005). A prerequisite of any system is that it is compatible with other systems in common use such as Read codes and International Classification of Diseases (ICD - 9/10) (Young, et al, 2001). A good example is the Intensive Care National Audit & Research Centre coding method which was developed empirically for coding the reason for intensive care admissions (Young et al, 2001; Harrison et al, 2004).

2.5.14 Data appraisal – local verses central measurement

It is preferable that the central database has responsibility for measuring outcomes, calculating scores and making judgements about data, to avoid information bias and improve data reliability. For instance the Intensive Care National Audit & Research Centre database requires all raw physiology data to be submitted to the database and all scores and probabilities are calculated centrally using standard algorithms to avoid any bias (Harrison et al, 2004). This data enables risk adjustment models to be derived using standard

algorithms across all units, allowing better comparability of risk adjusted outcomes between units. Additionally this method has the advantage of improving the utility of the database. For example if the data needs to be reanalysed to compare or complement other studies' results (i.e. a clinical trial) then having the raw data ensures it can be manipulated to fit the methods, definitions and scales used by other researchers (Padkin et al, 2003). Therefore because of the longevity and importance of databases/registries it is imperative they possess this compatibility and flexibility for optimal utility.

2.5.15 Sources of incomplete follow-up

Incomplete follow-up often happens because patient information is not accessed from sections of the health care system for example in outpatient departments, GP surgeries or for deceased patients. Therefore certain types of information such as drug treatment, timing of treatment and outpatient investigations may be systematically missed. Other variables may also be incomplete because follow-up is too short to capture all the relevant information or the abstractors have left the field blank because of problems interpreting the data due to poor documentation. Typical examples include staging disease, co-morbidity variables and diagnosis of late complications.

2.5.16 Impact of incomplete follow-up

Missing data can lead to non response bias because the patients with fields missing may be different to those included, for example the cohort with advanced disease or with mild disease (Worster and Haines, 2004). Therefore missing data, unless trivial, can threaten the validity of outcome analysis and results are not generalisable to the population. It may be possible to undertake statistical analysis to assess if non response bias has affected the results (Worster and Haines, 2004). For example a study reported by Wuerz (2001) conducted sensitivity analyses to test the effect of non-response bias on their results. Worster and Haines (2004) suggest comparing subjects not included in the analysis with those that are included to determine if they appear to differ systematically, such as by age or gender. These are not sufficient checks as participants who are included may differ in significant ways to non-participants even if they have a similar demographic profile (Al-Shahi et al, 2005; Tate et al, 2006).

Missing variables may limit the utility of the database if case-mix adjusted outcomes are prohibited. Norris et al (2000) found that improved completeness enhanced the performance of a clinical registry for predicting risk but it was only marginally better then when the analysis was conducted without the subjects with missing variables.

2.5.17 Methods to improve completeness of follow-up

The research shows that patients are treated in various health care facilities from diagnosis to end of treatment or death. The facility used by the patient depends on multiple factors including the type and severity of illness, therapy prescribed, residence and age. Therefore to capture complete and accurate follow-up multiple sources of relevant data need to be combined with sufficient length of follow-up. Developing a model of the likely patient journey through the health system will identify where essential data variables can be sourced. These may differ between sites therefore information on local clinical practices, such as shared care arrangements, should be recorded (Phekoo et al, 2002; Strobl et al, 2003). It is highly probable that it will not be possible to access data from all these sources due to logistical and resource constraints. However, if a primary source of data is not accessible, such as GP records, then it might be possible to collect the data from a secondary source. If underreporting of some information is known then it should be noted when reporting results (to assist readers with interpreting validity of results) (Du et al, 2006).

2.5.18 Effect of incomplete case ascertainment

Under ascertainment of cases leads to erroneously low estimates of incidence making it difficult to assess true risk or compare incidence rates between geographical regions (Berrino, 2003; Stefoski Mikeljevic et al, 2003). Additionally if completeness changes over time, for example after a quality audit, this can invalidate trend analysis in incidence or prevalence rates and should be acknowledged and adjusted for in the analysis, if possible (Topp et al, 1997; Bower et al, 2000).

The impact of under ascertainment on estimating outcomes is more complex. If missing cases are not representative of the population as a whole this introduces selection bias. In the case of cancer outcomes survival estimates can be over or under estimated, depending

on the severity of disease in the cohort excluded. For example if patients with advanced disease and poor prognosis are excluded then this would over estimate survival. This can invalidate comparisons between populations (Berrino, 2003). The effect of selection bias is more pronounced in subgroup analysis because of the small number of cases available for analysis. This may result in miscalculation in evaluation of the effectiveness of health programmes or lead to over or under provision of services for the population misrepresented. In contrast if cases are missing completely at random then the research and audit capacity of a clinical database in not unduly impaired (Every et al, 1999; Norris et al, 2000). Overall it is best to strive for a high degree of completeness of registration to have confidence in the registry. Any analysis published from registries should report the extent of incompleteness and its effect on incidence calculations or prevalence calculations, if appropriate.

Some statistical methods have been shown to reduce selection bias. For instance cancer survival rates are reported by age groups and the technique of age adjustment reduces the effect of selection bias on results (Brenner and Hakulinen, 2005). External validation studies can identify and quantify the probable extent of under-reporting and estimate the effect on reported incidence rates. There are also indirect quality indicators that can be applied to assess the completeness of a registry, such as the proportion of cases ascertained by death certificate only (Berrino et al, 1998). Stotter et al (2000) suggest that one should take into account how registry data was collected to assess validity of results.

2.5.19 Maximising case ascertainment

Multiple sources of information are the most efficient method of improving case ascertainment and verification to prevent false positives (Brewster et al, 1996; Stefoski Mikeljevic et al, 2003). Developing patient care pathways/scenarios of how affected patients are likely to be identified and treated can aid understanding of how to capture cases. This will be different for each disease therefore the best sources of information will differ for each clinical registry. For example a flagging system used by all radiologists reporting scans of the brain would identify virtually all cases of brain tumours (Pobereskin, 2001). In sickle cell disease this could be achieved by filtering patients by blood test results that are indicative of the disease. Another method is to get lists of all patients who attend

hospital clinics that are likely to have SCD patients and cross check the patients on the list with their blood test results.

Patients with mild disease are likely to have a different care pathway to moderate and severe cases and are often missed by registries because they might never be referred to hospital and/or admitted as an inpatient. Therefore for diseases with variable severity if outpatient and/or GP information are not captured this group of patients are likely to be under reported. Similarly severely ill patients who die shortly after diagnosis have a greater chance off not being identified because of their short utilization of health services. For other diseases, such as haematological malignancies, diagnosis is complicated and patients may be treated by a range of health professionals and therefore multiple internal sources of hospital information have to be amalgamated in order to identify and verify cases. Developing patient care pathways will also identify which health care professionals should be actively involved in the registry to ensure accurate diagnosis and improve case ascertainment and follow-up (Phekoo et al, 2002). Finally it is imperative to have knowledge of local clinical and reporting practices to maximise recruitment and interpret multi-centre data (Strobl et al, 2003).

2.5.20 Generalisability

Population based registries with low coverage can be included in aggregate (national, European wide) analysis provided the appropriate statistical methods are used to adjust for percentage of coverage. In the EUROCARE studies, countries that have less than 100 percent coverage are included in European cancer survival estimates by assigning weightings proportional to the reciprocal of the cancer registry's coverage in each country (Berrino et al, 1998, 2003). However if registries with low coverage are used in comparative analysis appropriate caution is needed with interpretation of the results, for example the likelihood of the data being representative of the geographical region (Berrino, 2003). While the results from the EUROCARE cancer studies suggest that registries with low coverage can be representative there is more confidence in the data the greater the coverage (Capocaccia et al, 2003). In addition clinical databases are prone to case selection and may not be representative of the underlying population (Capocaccia et al, 2003). Scrutiny of the exclusion/inclusion criteria will help identify if results are generalisable to the general population (Every et al, 1999). Overall it is better if all

potential participants in the targeted population have the opportunity of being included in the registry to avoid sampling and selection bias.

2.5.21 Quality assurance processes

Quality assurance programmes should involve both internal routine data quality procedures, to identify inconsistencies and missing data, and external validation checks of data reliability and completeness of registrations (Berrino et al, 1998; Fine et al, 2003; Pedersen et al, 2004). For example good reliability and completeness of cancer registries is indicated where a low proportion of cases have been identified by death certificate only; that the diagnoses where reliable is indicated by a high proportion of the cases confirmed by histological examination; and that follow-up was complete (Berrino et al, 1998).

In addition inter-rater and intra-rater reliability checks will identify problems with data abstraction such as ambiguous variable definitions and data elements or events difficult to identify in medical records (Chen et al, 1999; Eder et al, 2005). A pilot study at the outset should identify these problems for correction. However it would be prudent to carry out external validation checks periodically because over the lifetime of the database there will be staff changes, organisational setup may change and the dataset may be changed – all these things can have an adverse affect on data reliability.

Efforts should be made to improve the timeliness of data collection, processing and reporting so that registry results are more contemporary and relevant.

2.5.22 Government initiatives

Registry data in some of the Nordic countries is very complete and reliable and this is most probably influenced by the fact that registration of cases is mandatory and registries have a legal obligation to ensure that their data is complete and accurate. A similar climate of regulation and accountability for registry data is developing in the UK. Clinical registries and databases were recognised for their role in health surveillance, performance monitoring and facilitating patient choice when policymakers realised that improvements in health care could only be achieved when underpinned with good clinical information systems (Department of Health, 2000, 2007a). Some registries, such as the cancer registries

and the cardiac surgical databases, have already been mandated by the Department of Health and consequently became an integral part of the NHS development plans. This gave these registries the government support and resources needed to improve.

Registries are now expected to collect better quality and more comprehensive and timely information so they are capable of more than 'basic analysis' (Keogh et al, 2004; Department of Health, 2007a). This involves routinely collecting variables that have proved difficult in the past (e.g. staging of cancer, co-morbidity, complications of treatment) together with comprehensive Quality Accreditation Programmes to ensure high quality data (Society for Cardiothoracic Surgery in Great Britain & Ireland, 2005, 2008). The focus of current policy initiatives is to make it the responsibility of all clinical staff and agencies involved in patient care to ensure disease registries achieve this level of reliable information. For example the NHS Cancer Plan (2007) stipulated that multidisciplinary teams will have an important role to play in collecting all relevant clinical information for cancer patients and for making this data available for cancer registries and national audits (Department of Health, 2007a). Catalysts for change in the UK Cardiac Surgery Database were the recommendations of the Bristol Royal Infirmary Inquiry into paediatric cardiac deaths and growing government pressure, for public release of individual surgeon outcomes (Keogh et al, 2004). This was a powerful incentive to ensure information collected was comprehensive and reliable so that outcome and performance measurements were fair and accurate.

2.6 Conclusions

Population based registry information is now recognised as the linchpin to improvements in patient care. There is clear evidence that registry outputs can result in benefit to patients, health care providers and policy makers provided that their findings and recommendations result in local and national initiatives to improve patient care. A registry is a long-term investment and will result in increased benefits as the data collection period grows. However, registries are only as good as their data, which has proved to be of highly variable quality in the past. Therefore registries need to operate with the same scientific rigour as any other type of research study and report results and methodological deficiencies to ensure accurate interpretation. A clinical registry which functions as a clinical information system, in the context of clinical audit, is the best model for research, audit, health surveillance and routine patient management. This appears to be the only feasible method of collecting data for patients with chronic diseases, such as sickle cell disease, where outcomes, such as survival, cannot be related to a single intervention but to the efforts of a multidisciplinary team over a lifetime.

Chapter 3: Methodology

3.1 Introduction

This chapter will provide a brief history about the establishment of the sickle cell disease (SCD) registry at Central Middlesex Hospital (CMH) (section 3.1.1), the geographical coverage of the registry (3.1.2), local prevalence (3.1.3 and 3.1.4) and incidence of sickle cell disease (3.1.5). Section 3.2 provides an overview of the registry's function and organisation. Section 3.2.1 reiterates the aims and objectives of this thesis, section 3.2.2 describes the function of the registry and section 3.2.3 the registry properties. Section 3.2.4 provides an overview of the organisational set-up, section 3.2.5 covers ethical and data governance issues, section 3.2.6 the consent process and section 3.2.7 reports a procedure set up to overcome problems with access to patients' clinical information. The processes established for identification of SCD cases in the registry's catchment area are described under section 3.3, including the Newborn Screening Programme (3.3.1) and other screening methods (3.3.2). Potential and feasible methods of case ascertainment are described in sections 3.3.3 and 3.3.4. Development of a high quality registry is covered in section 3.4. The characteristics of high quality data are summarised under section 3.4.1, the proposed quality framework in section 3.4.2 and an overview of the data collection process in section 3.4.3. Methods for evaluating the utility of the registry are covered in the last section 3.5, including hydroxcarbamide (HU) measurable outcomes (3.5.1), monitoring HU adverse effects (3.5.2), patient eligibility and treatment schedule (3.5.3), data collection methods (3.5.4), data manipulation (3.5.5) and statistical methods and analysis (3.5.6).

3.1.1 Historical perspective

As stated in Chapter 1, the North West London (NWL) sector registry was established and curated at CMH. The registry initially covered the sickle cell patient population attending CMH and in 2001 three additional local hospitals joined (Hammersmith, Ealing and West Middlesex) thereby expanding coverage to three-quarters of the target SCD population. The care of SCD patients attending Northwick Park hospital was gradually moved to CMH in 2003, after rationalisation of services, when the hospitals merged to form the North West London Hospitals NHS Trust.

3.1.2 Geographical coverage

This geographical area encompasses the current NWL Sector Health Authority, which is the health district covered by the local Managed Clinical Network (MCN) for Haemoglobinopathies (Figure 3.1). This health district covers eight local authority boroughs and is serviced by nine acute hospital NHS trusts including CMH, Charing Cross (ChX), Chelsea and Westminster (C&W), Ealing (EGH), Hammersmith (Hamm), Hillingdon, Northwick Park (NPH), Saint Mary's (SMH), and West Middlesex University hospital (WMUH). Sickle cell patients who reside in NWL are expected to attend one or more of these hospitals for outpatient and inpatient care of their disease. Figure 3.2 shows the hospitals and the local authority boroughs these hospitals serve, the borough population, proportion of the population at significant risk of inheriting SCD and the estimated number of SCD patients attending each hospital. The Brent Sickle Cell & Thalassaemia Centre (BSCTC), located at the department of Haematology in Central Middlesex Hospital is a specialist centre for treating SCD patients. The centre serves the local population of Brent and Harrow and also receives patient referrals from other local hospitals and GPs in the sector as well as national and international referrals.
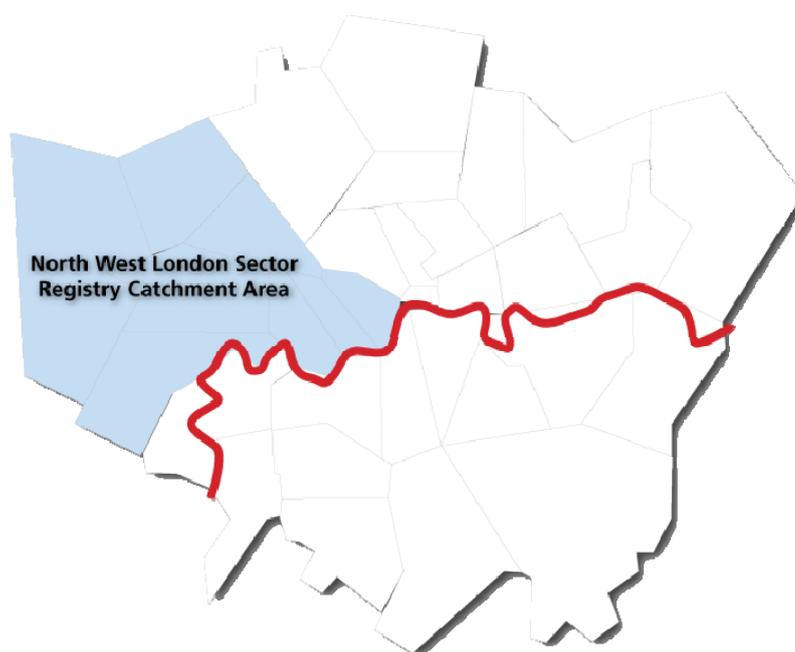
Figure 3.1: North West London Sector SCD Registry Catchment Area (London Boroughs)

The sector population is 1,731,019 and there are high rates of ethnic minority groups in each borough (ONS, 2003). Ethnic groups at greatest risk of inheriting the sickle cell gene, the black and black British, range from 20% in Brent to 3.3% in Hillingdon (Figure 3.2).

These groups include black Africans, black Caribbean and black Other minorities (Department of Health, 1993; Davies et al, 2000). In addition 45% of the sector's total population consists of ethnic minority groups that have varying degrees of risk of carrying the sickle or thalassaemia gene (Davies et al, 2000; ONS, 2003). For instance Brent scored as the most ethnically diverse local authority area in England and Wales in the 2001 Census, with an 85% chance that two people chosen at random would be from different ethnic groups.
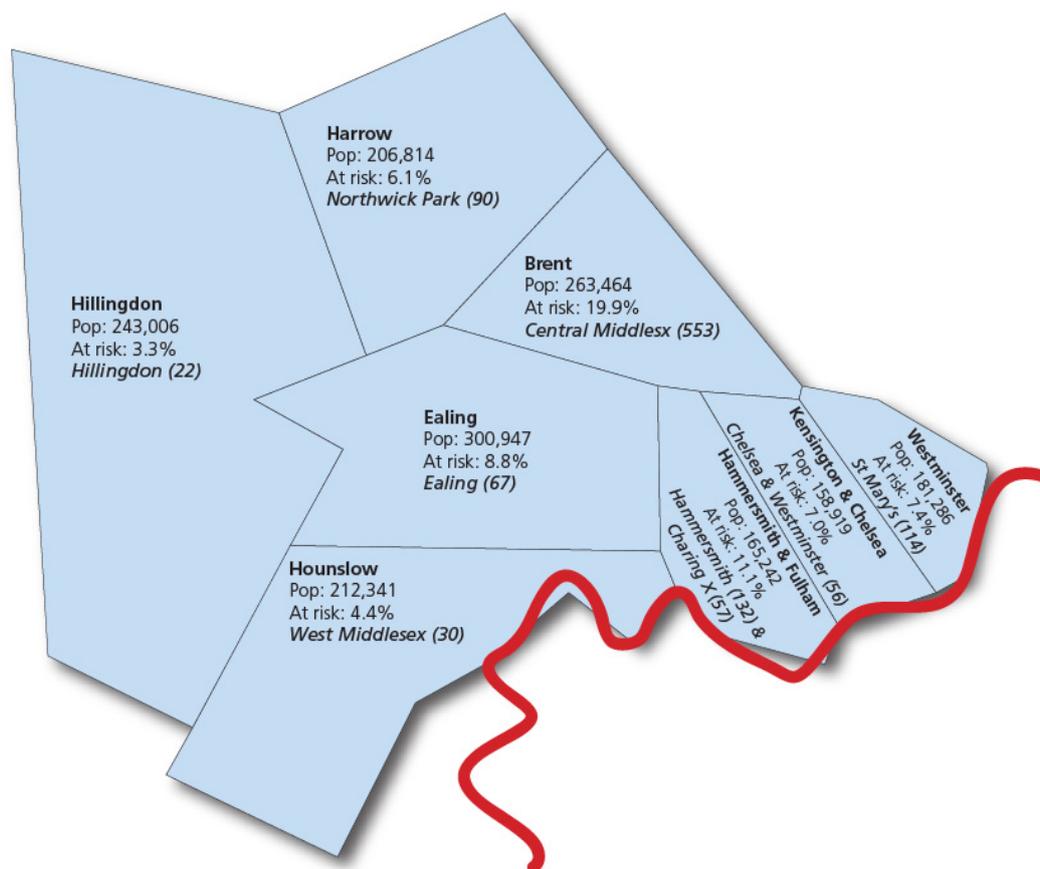
Sources: *2001 Census for England and Wales
*At Risk Population = Black African, Black Caribbean and Black Other Ethnic Groups
#Alli M (2002) Haemoglobinopathy MCN for NWL: 3 Year Delivery Plan 2003-06

Figure 3.2: NWL Sector SCD Registry Catchment Area (London Boroughs) Population Estimates and % at Risk of SCD (Trait or Disease*) NHS Acute Hospital Trusts Located in Each Borough (Est. No. SCD Patients#)

3.1.3 Prevalence

Due to the local concentration of ethnic groups at risk of inheriting this disease, it is reasonable to expect that high numbers of people with sickle cell reside in the NWL health district and use the health services therein. Disease prevalence arises from both migrants that have the disease and from affected births in the settled immigrant 'at risk' populations.

Most immigration into Brent occurred during the 1950s and was from the Caribbean and Pakistan (Davies et al, 2000). Immigration from Africa occurred later and continues to the present day. Therefore Brent would be expected to have a mixture of first, second and third generation migrants with the disease.

There are no reliable estimates of the number of people with sickle cell in NWL. The best information was derived from a questionnaire survey of all haematologists and paediatricians looking after haemoglobinopathy patients in the nine acute NHS hospital trusts in NWL (Figure 3.2). This data suggests that in 2002 there were approximately 1113-1172 patients with SCD attending the local hospitals, of which 530 attended Central Middlesex (Alli, 2002). These figures lack precision because they were derived from the clinician's best guesstimate of patient numbers in their clinics. Also only patients who are known to the haematologist or paediatrician were included so patients who have not been referred by their GPs to a clinician for care of their sickle cell would be missed as would those who have never been diagnosed with the disease.

3.1.4 Derivation of SCD prevalence statistics for NWL

In order to get a more precise estimate of prevalence rates I have derived a population based estimate from the 2001 census statistics using the rates of disease among ethnic minority groups calculated by Davies et al (2000). This estimate, shown in Table 3.1, is more comprehensive than Alli (2002) but it also has deficiencies. For example it has not been age adjusted to take account of the declining rate of disease with age due to premature death in SCD. Conversely rates of disease could be higher than expected in NWL because people with the disease are more likely to come to a country (and area) which provides good health care for their condition and these individuals are also more likely to be granted permanent residency due to their medical needs. In addition a few cases will be missed because the rate of disease in other ethnic groups has not been considered in the estimate, though this number is very small. Overall the expected number of sufferers in NWL is between 1172 and 1468, probably closer to the higher estimate. Using the population estimates from Table 3.1 the prevalence is between 1172/151,671 and 1468/151,671 [between 0.0077 = 7.7 per 1000 at risk population and 0.0097 = 9.7 per 1000 at risk population]. To simplify and round up between 0.8% and 1% of the at risk population have SCD.

Table 3.1: North West London Sector Sickle Cell Disease Registry: Population at risk, estimated prevalence of SCD and current estimate of patients attending hospitals in NWL

Local Authority Borough	Total pop.	Census 2001									Total SCD pop.	Alli, 2002	
		% Black African	Pop. Bl African	*Estimate SCD pop.	% Black Caribbean	Pop. Bl Caribbean	*Estimate SCD pop.	% Black Other	Pop. Bl Other	*Estimate SCD pop.		Acute hospital	Estimate SCD pts attending
Brent	263,464	7.83	20,629	303	10.47	27,585	154	1.56	4,110	23	481	CMH	553
Ealing	300,948	3.68	11,075	163	4.49	13,513	76	0.62	1,866	10	249	Ealing	67
Hammersmith & Fulham	165,242	4.88	8,064	119	5.16	8,526	48	1.08	1,785	10	176	Hamm	132
												Charing X	57
Harrow	206,814	2.73	5,646	83	2.96	6,122	34	0.45	931	5	122	NPH	90
Hillingdon	243,006	1.74	4,228	62	1.35	3,281	18	0.21	510	3	83	Hillingdon	22
Hounslow	212,341	2.7	5,733	84	1.33	2,824	16	0.32	679	4	104	WMiddx	30
Kensington & Chelsea	158,919	3.78	6,007	88	2.58	4,100	23	0.61	969	5	117	C&W	56
Westminster	181,286	3.68	6,671	98	3.1	5,620	31	0.66	1,196	7	136	SMH	114
												Not known	59
Total at risk of SCD:			68,054	1,000		71,570	401		12,047	67	1,469		1,172

Population statistics from 2001 Census (ONS, 2003).
Numbers of patients attending acute hospitals in the sector are from Alli (2002)
* Estimates of SCD population are calculated using the rates of disease derived by Davies et al, 2000

Estimating rates of disease: (Source Davies et al (2000)
1. High carrier rates are responsible for high rates of disease among black ethnic minorities:
0.11 Carrier rate S and 0.04 carrier rate C leads to 5.6 per 1000 births among black Caribbeans
0.20 Carrier rate S and 0.03 carrier rate C leads to 14.7 per 1000 births among black Africans
0.11 carrier rate S and 0.04 Carrier rate C leads to 5.6 per 1000 births among black Other

3.1.5 Incidence

The North West Thames Regional Neonatal Screening Programme figures, for the period 1990 to 1994, show that there was an annual mean rate of 25.5 SCD births in the whole region with a mean of seven for Brent (Davies et al, 2000). The geographical area covered by the programme is wider then the NWL health sector but most of the affected births occurred within the sector. The majority of these babies will be cared for by their local hospital within NWL or referred to a specialist centre within the region. The few children born outside the sector boundary (Barnet and Bedford) are likely to be looked after by their local hospital but referred to a specialist centre in NWL, such as Central Middlesex Hospital, for annual monitoring or specialist advice. These informal shared care arrangements between hospitals will be formalised in the future as the national standards for caring for sickle patients recommend that all sickle patients should have their care overseen by specialist sickle centres and have access to specialist centre services as required (NHS Sickle Cell and Thalassaemia Screening Programme, 2006b; Sickle Cell Society, 2008).

In addition people with sickle cell move into the sector each year due to the migration pattern of ethnic minorities; they tend to move into areas where there are people from the same background and to be near relatives (Sanchez, 2004). There is no available estimate of these numbers or of the stability of these population groups within the sector. However comparison of the 1991 and 2001 census statistics shows that both the number of people at significant risk of sickle cell is increasing in NWL and they are an increasing proportion of the total population (Table 3.2). Brent had the biggest increase (3.5%) where the 'at risk' group rose by 12,594. The 'at risk population' also rose considerably in the London borough of Harrow by 5294 (2.44%).

Table 3.2: North West London Sector Sickle Cell Disease Registry: Estimated population at risk of SCD in 1991 and 2001

Local Authority Borough	Total population	* % pop. at risk	Total pop. at risk	Total population	* % pop. at risk	Total pop. at risk
	1991	1991	1991	2001	2001	2001
Brent	243,025	16.5	40,099	263,464	19.86	52,324
Ealing	275,257	7.1	19,543	300,948	8.79	26,453
Hammersmith & Fulham	148,502	10.2	15,147	165,242	11.12	18,375
Harrow	200,100	3.7	7,404	206,814	6.14	12,698
Hillingdon	231,602	1.7	3,937	243,006	3.3	8,019
Hounslow	204,397	2.7	5,519	212,341	4.35	9,237
Kensington & Chelsea	138,394	5.8	8,027	158,919	6.97	11,077
Westminster	174,814	7.6	13,286	181,286	7.44	13,488
Total:	1,616,091	0.07	**112,962**	1,732,020	0.088	**151,671**
% of total population:		7%			8.8%	

* The main population groups at significant risk of SCD are black African, black Caribbean and black Other ethnic minorities.
Sources: 1991 Census (ONS); 2001 Census (ONS, 2003); Davies et al (2000)

3.2 Method of Evaluation

3.2.1 Aims and objectives

To reiterate, the aim of this study is to evaluate the feasibility and utility of the SCD database or registry for clinical management and research. The specific objectives are to:

    i.   Develop an evidence based registry
    ii.   Ensure high quality data
    iii.   Identify and develop clinical management tools from the registry data
    iv.   Demonstrate utility of the registry for SCD patient management and research

3.2.2 Registry function

The review of the literature, in Chapter 2, suggests that the role of a clinical registry/database is to describe the health and health care of the population under study. It is an essential information source which should act as a catalyst for change and improvement or as proof that a service or treatment is effective. To be of value a registry needs high quality, usable and relevant information (Department of Health, 2007a). The intended use(s) of the sickle registry should be decided a priori as this determines the necessary properties of the data to be collected (Arts et al, 2002). In addition the quality of the data determines how well the registry may be utilized. As discussed in Chapter 2, section 2.5.11, paragraph 4, the degree of data accuracy influences the level and type of analyses that can be conducted; the better the data the fewer the constraints (Middleton et al, 2000; Brewster et al, 2002; Fine et al, 2003; Keogh et al, 2004).

3.2.3 Registry properties

All patients with SCD in the target population should be included for measuring prevalence and incidence rates. SCD is an inherited chronic disease and therefore the database should have the ability to follow-up patients over their lifetime in order to describe the natural history of the disorder. It should also be able to monitor and follow-up sub-groups of patients prescribed new treatments to assess long-term benefit versus risks. Patients on hydroxycarbamide treatment will populate the HU sub-registry. To illustrate the natural history of SCD and/or evaluate the effectiveness of a health technology the dataset should include all the patient characteristics that affect outcome. Complete case ascertainment is of lesser importance for these uses (Sørensen et al, 1996).

3.2.4 Organisational principles of the SCD Registry

In order to establish and maintain a successful SCD registry the following organisational structures and processes were developed.

    i.   Overseen by a NWL sector steering/management group.
    ii.   Involvement of the multidisciplinary team.
    iii.   Continuous efforts to maintain funding streams.

3.2.5 Ethical Approval and data governance

As stated in Chapter 1 the registry has research ethics committee (previously known as multi-centre research ethics committee (MREC)) approval to conduct research on the data collected. The approval number is MREC/99/2/4. In addition the project is registered under the UK Data Protection Act (registration number: Z5730583) for the purpose of collecting patient demographic and clinical information for research.

3.2.6 Consent procedure

The research ethics committee (REC) approval requires that the patient gives informed written consent prior to utilization of their data for research purposes. The practical obstacles to gaining consent and the methodological implications for the research caused by exclusion of non consenting patients were described in Chapter 2. The following strategy was implemented to maximise consent rates:

i.   Obtain consent from patient/carer during designated sickle cell outpatient clinic visit.
ii.   Involve multidisciplinary sickle cell team to obtain patient consent (doctors, nurses, researchers).
iii.   Develop tools to assist with the consent process (for example list of consented patients, label to mark notes when patient has consented).
iv.   Monitor consent rates.
v.   Identify factors that influence whether patients consent or not.
vi.   Utilize an audit cycle to improve process by targeting deficiencies in the process.

A regularly updated excel list was created to monitor rates of consent, factors that influence the rate of consent such as mean numbers of visits required to gain consent and reasons for non consent.

3.2.7 Clinical information retrieval

In retrospective study designs there are problems accessing deceased patients' medical records. Indeed this also applies to living SCD patients as they are likely to accumulate numerous volumes of notes throughout their lifetime. Therefore a separate archive system

was established to have easy access to all SCD deceased patients' medical notes and non-current (closed) notes for surviving patients.

3.3 Disease detection in North West London Health Sector

3.3.1 Newborn Screening Program

As stated in Chapter 1 sickle cell disease is detectable from birth using a specialist blood test. Universal neonatal screening for sickle cell and thalassaemia was introduced in North West London in 1988 and covered the old North West Thames Regional Health Authority (Davies et al, 2000). Initially both first and second line screening tests were undertaken in the Regional Haemoglobinopathy Laboratory at Central Middlesex Hospital. After the establishment of the national SCD newborn screening programme first line screening moved to Great Ormond Street Hospital, in September 2003, and second line testing remained at CMH. The positive test results (both trait and disease) are sent to the Specialist Community Nurses in BSCTC for follow-up. This geographical area encompasses the current NWL Sector Health Sector and the NWL SCD registry.

All neonates born in the district have been screened for sickle cell disease since the programme began in 1988. All affected babies have been referred by the BSCTC to the haematologist or paediatrician in their local hospital for follow-up clinical care. The baby's GP, health visitor and the child health department are sent written confirmation of the diagnosis. The CMH haemoglobinopathy laboratory services have changed since the introduction of the national SCD newborn screening programme but this has not affected the identification of and follow-up care programmes for local babies born with sickle cell.

3.3.2 Other screening modes

Local universal and targeted antenatal screening programmes in the health district identify a small proportion of adults with sickle cell. Other individuals are picked up, as discussed in Chapter 1, by family screening, symptomatic presentation to local health services or during routine screening such as pre-operatively. Individuals are also detected if they self present for a screening test to the GP or to the local specialist haemoglobinopathy community nurses. All screening blood tests, apart from those undertaken as part of the

neonatal screening program, are undertaken in the haematology laboratory of a local hospital. If the local laboratory is unable to undertake the test then it is sent to another laboratory in the area and results are sent back to the referring laboratory.

3.3.3 Potential modes of case ascertainment

Figure 3.3 shows the patient screening pathways where cases with sickle cell disease, in NWL, are diagnosed. The screening laboratories are the primary source for identifying cases because definitive diagnosis is made by a specialist blood screening test. The test preformed is haemoglobin electrophoresis or high performance liquid chromatography (HPLC). The newborn screening programme uses both tests to confirm diagnosis; HPLC for first line testing and haemoglobin electrophoresis for second line testing (Old, 2007). Additional information, such as family studies and DNA analysis, is required for some types of sickle cell disease diagnoses. Testing for thalassaemia also involves review of the person's full blood count (FBC) indices and evaluation of clinical symptoms (Old, 2007).

As shown in Figure 3.3 the screening tests for all newborn babies in the region are undertaken by the Regional Haemoglobinopathy Laboratory at CMH and therefore this is the best source for identifying babies, born in the district, with SCD. All other cases will be diagnosed by the local haemoglobinopathy or haematology laboratories in the region. For example the cases in Brent and Harrow will be diagnosed by CMH because it is the local laboratory where blood specimens are sent from resident GPs, hospital departments and the BSCTC Community nurses.

Unfortunately it is not possible to use this method as the primary source of case ascertainment to populate the NWL SCD registry primarily because of the financial cost and IT expertise required to extract the data efficiently and securely. The aim, in the long term, should be to include this data source to enhance the completeness of case ascertainment.
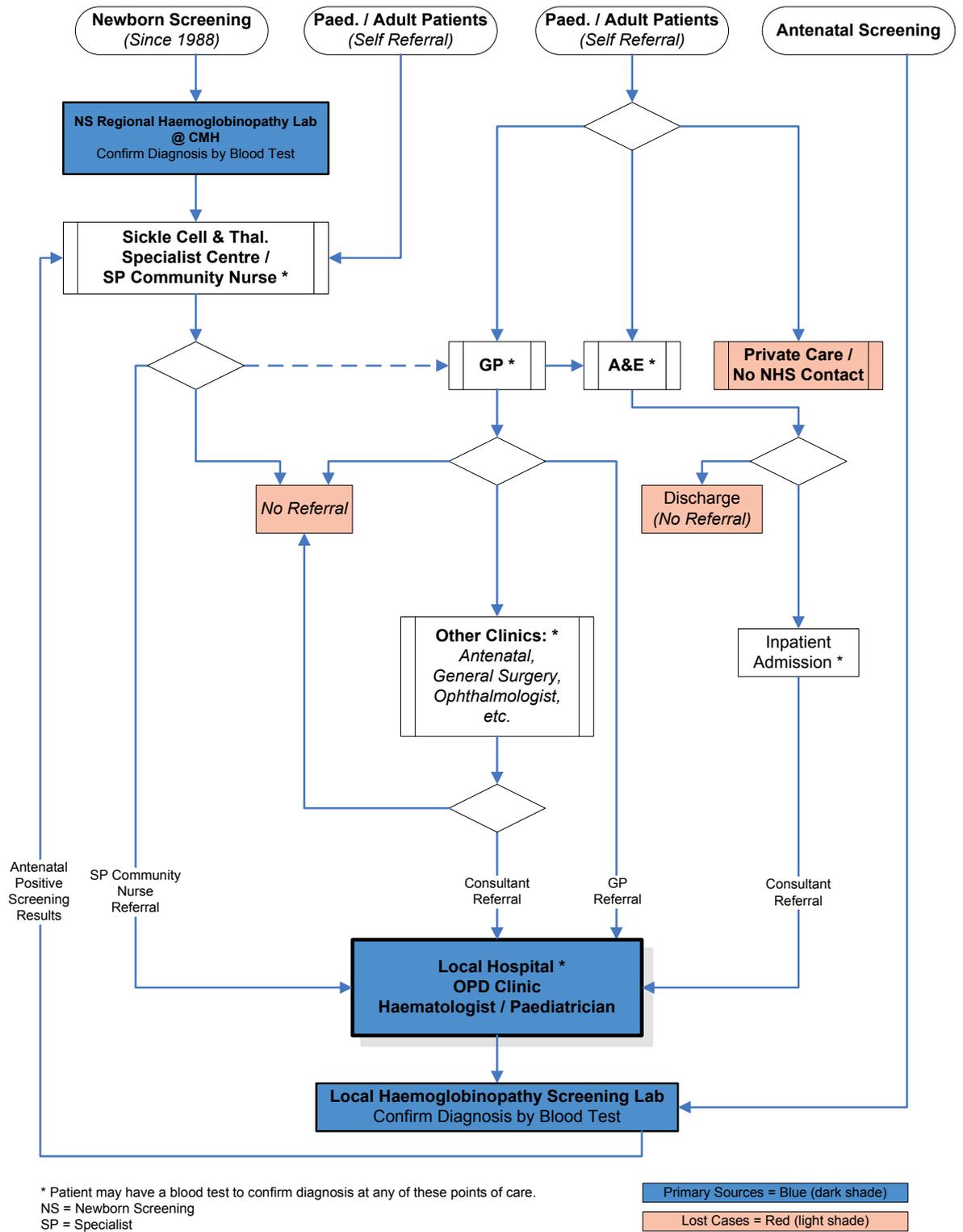
Figure 3.3: Sickle Cell Disease Patients in North West London Sector: Primary Information Sources for Case Ascertainment

3.3.4 Primary method of case ascertainment for the NWL SCD registry

In the case of chronic diseases, such as sickle cell, there is frequent repeat contact between health care providers and the individual. Figure 3.3 describes all the potential pathways where SCD cases come in contact with the NHS. When a patient has been identified with the disease they should be referred to the haematologist or paediatrician in their local hospital or local specialist SCD centre for outpatient follow-up care. Patients with sickle cell disease have stable conditions with intermittent acute exacerbations. The majority regularly attend designated outpatient clinics for monitoring. Consequently the local sickle cell clinics in each hospital, within the health sector, are the next most efficient sites for identification of cases. Patients are generally well/ in steady state condition when they attend outpatients therefore this is the best time to inform them of the registry, gain their consent and initiate data collection.

A small minority are missed if they are not referred to the SCD clinic or are referred and do not turn up. Patients that use private healthcare exclusively will also be missed but they are likely to be non UK residents and are therefore ineligible to join the registry.

3.4 Development of evidence based high quality registry

The major threat to the viability and utility of a registry/database is the quality and 'perceived' quality of the data. Clinicians and users of the data must have confidence in the quality of the registry both to make use of registry outputs and to be motivated to collect data for inclusion in the registry (Black and Payne, 2003; Raftery et al, 2005). Therefore the quality of the data plays a central role in determining the feasibility and utility of the database for the benefit of sickle cell patients. According to the literature (see chapter 2, section 2.5.11, paragraph 4) the proposed purpose of the specific data collection dictates the quality attributes that must be achieved. Abate et al (1998) suggest that an acceptable level of data quality is achieved if it conforms to a defined specification and the specification correctly reflects the intended use. If the data satisfies these quality indicators, called conformance and utility, then the data agrees with international and traditional standards for data quality and is 'fit for purpose' or 'fit for use' (Abate et al, 1998).

3.4.1 Data quality characteristics for a SCD registry

Assuring data quality requires establishing quality assurance procedures and quality control processes (Arts et al, 2002). Quality assurance consists of activities undertaken before data collection to ensure that the data collection is optimised. Quality control occurs during data collection to identify and correct substandard and/or erroneous data (Whitney et al, 1998). The data quality attributes that constitute a high quality SCD registry must be defined in order to develop quality assurance and quality control processes (Arts et al, 2002). The literature identified the following data quality characteristics that infer high quality:

- complete coverage of the target population
- complete case ascertainment
- complete and accurate data variables collected for each case
- outputs that are relevant, timely and usable
- adds value (beneficial to patients, health care providers and service planners)

3.4.2 Quality assurance framework

An operational framework has been developed to optimise quality of data collected by the registry. The framework, outlined in Table 3.3, describes the quality attributes that are required in relation to the purpose of the registry data (1st column). Column 2 defines the methods and processes established to enable the quality criteria to be achieved and the third column outlines the methods for evaluating if they are achieved. The outcome measures selected are objective, feasible, and can be repeated to monitor progress over time. Table 3.4 is a plan of the operational procedures implemented and tools developed to achieve the goals outlined in Table 3.3.

Table 3.3: Operational Framework for Quality Assurance and Evaluation of Sickle Cell Registry

Registry Aim	Quality Criteria	Operational Methods	Measurement criteria
Incidence and prevalence data	1. Total coverage of target population 2. 100% case ascertainment 3. Diagnostic accuracy 4. Accurate and complete demographics and diagnosis	**Completeness of Case Ascertainment** • Collaborate with local health professionals and PCTs. • Map geographical area with % (no.) of target population at risk. Estimate total no. cases as reference data. • Map patient pathway for diagnosis and treatment to: • Define case identification methods and • Define sampling method.	a) % of target population included. b) No. patients recruited vs total. c) Utility - e.g produce incidence and prevalence data reports, d) Identify cases for inclusion in research/audits

Natural History of SCD	Criteria 1 to 4 and:
	5. Collect data on all patient characteristics that affect outcome.
	6. Accurate and complete clinical data collection.
	7. Data collector blinded to hypothesis; objective outcomes
	8. Data validation process:
	  a) internal checks
	  b) external checks.
	9. Completeness of follow-up.
		Completeness and Accuracy of registry data
		• Develop minimum datasets
		• Map patient care pathway to identify sources of data and personel responsible for care.
		• Decide data collection methods, processes and tools.
		• Develop quality assurance tools and processes.
		• Develop data quality checks - automated and manual.
		• Undertake external validity checks.
		• Define patient follow-up procedures.
			e) Utility - observational studies with
			f) Discussion of patients lost to follow-up and reasons why.
			g) Quality assurance - development of tools and processes,
			h) Quality checks- quality reports e.g % missing data for demographic and clinical variables.
			i) Conduct external data validation- inter/intraobserver reliability studies.

Evaluation of health technologies (Hydroxycarbamide)	Criteria 3-9.	• Develop HU datasets and data collection methods.	j) Utility - observational study of long- term clinical benefit of HU. k) Conduct checks on HU sub- registry data as outlined in f)-i).
Patient management and audit	Criteria 3 -9.		l) Produce patient clinical reports. m) Produce aggregate demographic and clinical reports as required.
Service planning and monitoring	Criteria 1- 4 and 9.		n) As for c) and m) above

Table 3.4: SCD Registry Quality Assurance Methods

Sampling Method
- Create comprehensive list of all known eligible patients (with sickle cell disease diagnosis)
- All consecutive cases selected after site joins registry
- Inclusion criteria:
  - All patients with a significant SCD diagnosis (SS, SC, SBthal, SD, SO)
  - Patient attends participating hospital as an outpatient or inpatient
- Exclusion criteria:
  - Failure to obtain consent

Hydroxycarbamide (HU) sub-registry
- Inclusion criteria:
  - All children and adults with SCD treated with HU

Quality Assurance Procedures
- Develop evidence based datasets for data collection
- Develop guidelines for proforma completion
- Develop glossary of study definitions for clinical events
- Data extraction: blinding to hypotheses and/or objective outcome measures
- Abstractors are health professionals or health care employees
- Abstractors receive training, ongoing supervision and support
- Consensus management of conflicting and 'difficult to interpret' data
- Easy access to data collection tools for all sites and personal - via registry website
- Ongoing communication with sites and staff involved in registry

Quality Control Procedures: Internal
- Second check of data collected/ or sample of each patients data rechecked
- Automated data validation and processing
- Return draft patient report and log to abstractor for verification and completion of missing and/or conflicting information
- Produce descriptive statistic reports of data quality (e.g. % missing data for selected variables and cases)

Quality Control Procedures: External
- Conduct reproducibility studies (to assess inter and intra-observer reliability)

3.4.3 Principles of Data collection

I. The data collection set included patient demographics, diagnosis and disease stage data, co-morbidities, risk factors, treatment details and outcomes of interest. These were the fields identified in Chapter 2 as critical for data collection. A supplementary set of data variables were collected in the HU sub-registry. This data set will be described in the next section.

II. Triangulation of data sources is the most reliable method of increasing data reliability and data completion rates. A hierarchy of data sources were developed, shown in Table 3.5, to identify the primary and secondary supplies of valid data. This was based on the systems available at CMH but it can be applied to any hospital in the area. In situations where the registry was unable to access the best source of data due to physical, financial or other barriers then lower levels of data were used. In addition there were some localised differences between hospitals in how to access some information.

III. The extra workload was reduced by spreading the data collection among all relevant health care team members and electronic record retrieval, where feasible. Care pathways identified which health care professionals should be actively involved to ensure accurate diagnosis, improved case ascertainment and follow-up (Figure 3.4 and Figure 3.5). Data collection was initiated in outpatients during regular or annual clinic review. The medical team were primarily responsible for gaining patient consent and collecting the prospective data. The nurses and registry co-ordinators were also involved. The registry co-ordinators managed the registration of patients and data collection processes and collected retrospective data where required.

Table 3.5: Data Collection for Sickle Cell Disease Patients:Hierarchy of Information Sources

Hierarchy	Demographics	Diagnosis	Past Medical History	Family History	Clinical Examination
1	Patient Administration System (PAS)	Blood Test Results Database	Patient medical notes	Community Nurse casenotes	Patient medical notes
2	Patient medical notes	Hospital Intranet Reporting system	Patient Interview	Patient medical notes	
3	Patient Interview	Patient medical notes	GP medical records	Patient Interview	

Hierarchy	Current Treatments	Current Medications	Current Medical Problems	Psychosocial	Outpatient Activity
1	Patient medical notes	GP medical records	Patient medical notes	Patient medical notes	Patient Admin. System
2	GP medical records	Pharmacy Database	Patient interview	Community Nurse casenotes	Patient medical notes
3	Patient interview	Patient medical notes			
4		Patient interview			

Hierarchy	Inpatient Activity	Inpatient Diagnosis	Immunisations	Allergies	Blood Results
1	Patient Admin. System	Patient medical notes	Child Heath Database	GP medical records	Blood Test Results Database
2	Patient medical notes	Electronic Discharge Summary	GP medical records	Patient medical notes	Hosp Intranet Reporting system
3	Hospital Episodes Statistics (HES)	Hospital Episodes Statistics	Baby book (Red book)	Patient Interview	Patient medical notes
4	Patient interview	Patient interview	Patient medical notes		
5			Patient Interview		

Hierarchy	Radiology (X-Rays, USS)	Sleep Study	Lung Function	TCD Scanning	Other Investigations
1	PACS Database	Patient medical notes	Lung Function Database	TCD Database	Pathology Database
2	Hospital Intranet Reporting system	Sleep study database	Patient medical notes	Hosp Intranet Reporting system	Hosp Intranet Reporting system
3	Patient medical notes			Patient medical notes	Patient medical notes

Hierarchy	Vital Status	External Test Results	Extra Research Data
1	Office of National Statistic (ONS)	Patient medical notes	Patient Interview
2	GP medical records	Patient Interview	Patient medical notes
3	Mortuary Database/Notes	Other Hospital	
4	Patient Admin. System	GP medical records	
5	Patient medical notes		

Key: **TCD = Transcranial doppler**   **GP = General (Medical) Practitioner**
        USS = Ultrasound Scan
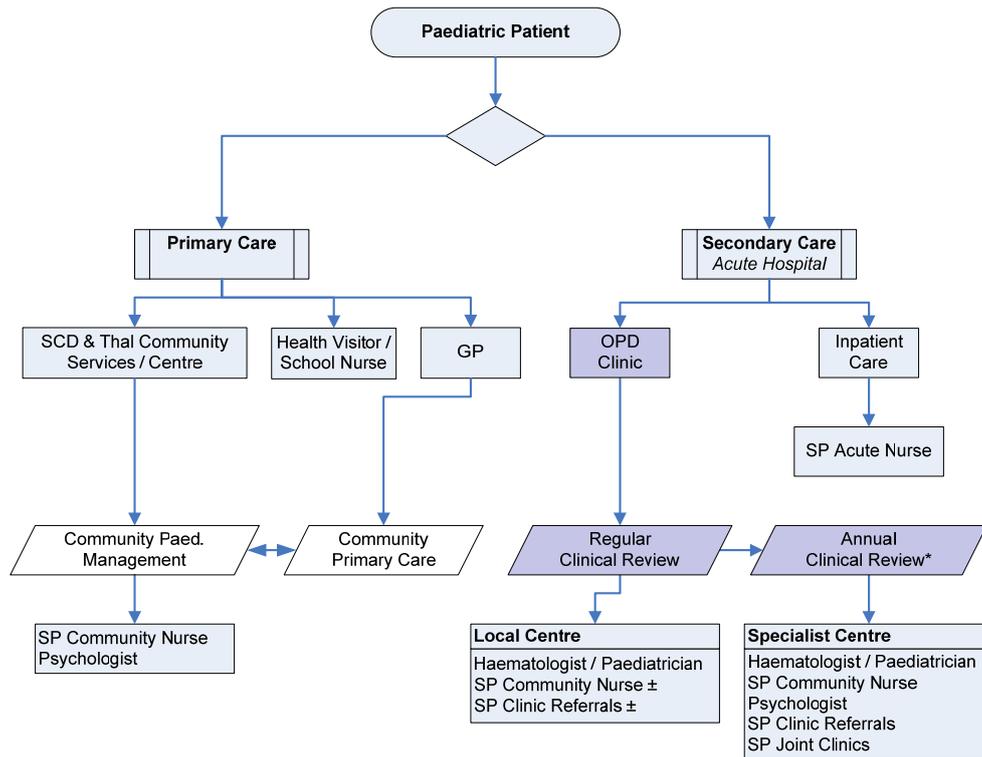
* Annual clinical review undertaken at local and specialist centre. Patient may be referred to specialist centre more frequently as required.
SP = Specialist

Figure 3.4: Sickle Cell Disease Paediatric Care Pathway
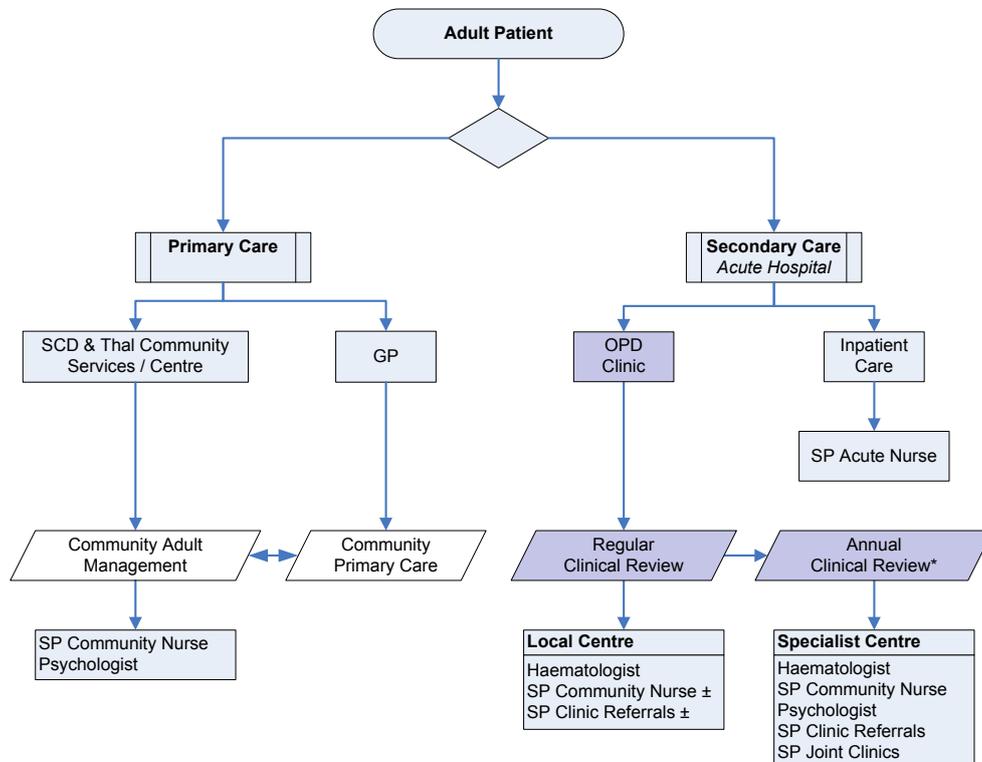
* Annual clinical review undertaken at local and specialist centre. Patient may be referred to specialist centre more frequently as required.
SP = Specialist

Figure 3.5: Sickle Cell Disease Adult Care Pathway

3.5 Utility of the SCD Registry

The hydroxycarbamide (HU) sub-registry was used to evaluate the utility of the database for research and clinical care purposes. This study evaluated the long term effectiveness and safety of hydroxycarbamide treatment for SCD patients. In addition this data was utilized for clinical management by the production of patient reports for monitoring treatment.

3.5.1 Hydroxycarbamide: measurable outcome indicators from therapy

The measurement parameters used in this study have been defined from existing research for monitoring HU treatment efficacy. In particular the indicators used by the Multicentre Study of Hydroxyurea (MSH) (Charache et al, 1995) continue to be used for estimating haematological and clinical response both in research studies and for clinical monitoring during therapy (Ohene-Fremprong and Smith-Whitley, 1997; Davies and Gilmore, 2003; Halsey and Roberts, 2003). Other research studies, especially in children have evaluated additional clinical outcomes. Using the same outcomes as other studies facilitates comparison. A further criterion for inclusion of a variable was the ability to collect and measure the variable in routine clinical practice. The same parameters were used for clinical monitoring during therapy therefore the database could function as a clinical management tool as well as a research resource. Table 3.6 describes the biologic variables measured, the rationale for using the variable and how the change induced by HU benefits the patient. Table 3.7 outlines the clinical outcome variables evaluated and the rationale for their inclusion.

Table 3.6: Measurable outcomes: Biologic parameters

Parameter	Rationale for using parameter	Benefit to patient
HbF% ↑ Δ in F% from baseline value	• HU ↑ the production of HbF. [1,2] The HbF in F cells inhibits sickling. ↑ in HbF reduces HbS concentration and inhibits polymerization of deoxygenated HbS in RBCs. [2,3,4] • Routine test, measured from full blood count (FBC) blood sample.	Patients with the highest HbF levels have fewer pain crises and live longer. [4,6,7,8] The best clinical and haematological responses were observed in patients with the largest rise in HbF%. [5,10] but benefit of HU is not only attributed to ↑in HF. [2,9,10] May be useful in measuring compliance. [2,10]
MCV ↑ Δ in MCV from baseline value	• HU causes macrocytosis. [11] • Δ HbF% is strongly correlated to Δ in MCV. [5,10,12] • Routine test, measured from FBC blood sample.	Shown to be a significant factor in predicting crisis rate. [10] May be useful in measuring compliance. [13] Suggested as an index of the overall pharmacological effect of the HU treatment. [5]
Total Haemoglobin ↑ Δ in Hb from baseline value	• HU ↓ anaemia due to reduced haemolysis. • Simple method to measure haematological benefit of HU. [15] • Routine test, measured from FBC blood sample.	Severe anaemia is a marker of severity in SCD therefore an ↑ in steady-state haemoglobin (Hb) is clinically beneficial (if associated with an ↑ in HbF%). [15] Most childrens' studies found a significant ↑in Hb. [14] Some studies achieved a mean rise in Hb of ≥ 1.2 g with HU. [15]
Reticulocytes ↓ (retics)	• ↓Retics causes ↓cellular adhesion to the endothelium. [14,17] • Some studies suggest baseline retic level is a proxy measure of bone marrow reserve. [16] • Measured from FBC sample, routine test.	HU ↓ the retic count rapidly and this is thought to be related to the quick clinical improvement observed well before the patient's Hb F rises to maximum level. [14,17] Response to HU, as measured by ↑ in HbF is highly correlated to response to MCV, neuts and retics. [2] Significant reductions have been observed in most studies. [2,14,18]
Neutrophils ↓ (ANC/neuts)	• Influence of WBCs ↓ not well understood. • Neutrophils cause tissue damage during an inflamatory response such as during a crisis therefore ↓ will be beneficial. [10] • Suggested as proxy measure of bone marrow reserve. [16] • Measured by WBC differential analysis. • Routine test, measured from FBC blood sample.	It is thought that neutropenia causes a smaller infarct if a vaso-occlusive event occurs and the pain crisis is reduced. [10] It has been suggested that ↑ ANC may be part of the mechanism producing crisis, ACS and even death in SCD. [10] ↓WBCs have been shown to be associated with ↓ ACS events and prolonged survival. [7,15] Shown to be significant factor in predicting crisis rate. [10] Significant reductions have been observed due to HU. [14]
Total Bilirubin ↓	• Bilirubin ↑ in SCD due to ↑ haemolysis. HU delays and reduces RBC destruction thereby reducing haemolysis. [20] • Measured as part of routine liver function tests.	Haemolysis causes sickle complications therefore beneficial to reduce. [15] Significant reduction observed in some studies, especially when HU used at maximum tolerated dose. [5,14,18,19,20]

Note: Δ = change (i.e HbF%final - HbF%initial)
MCV = Mean cell volume, Hb = haemoglobin, retic = reticulocyte, ANC = absolute neutrophil count, WBC = white blood cell, RBC= red blood cell.

Table 3.7: Clinical outcome parameters

Parameter*	Rationale for evaluation
↓ frequency of hospitalized pain crises events	MSH found significant reduction in adults and a ↓ was observed in children studies. [14,19,21]
↓ frequency of ACS events	Significant reduction observed in MSH and in some studies of children. [14,19,21,22,23]
↓ in annual number of inpatient days	↓ found in childrens studies. [14,19]
↓ in annual number of inpatient admissions	↓ found in childrens studies. [14,19,22]
↓ Blood transfusion (Tx) requirement	In MSH significantly fewer patients on HU required a Tx. [21] Some childrens' studies report ↓ in patient's Tx requirements. [14,19]

* The evaluation will measure the annual change in clinical outcome from baseline value

3.5.2 Monitoring hydoxycarbamide adverse effects

Hydroxycarbamide is a potent chemotherapeutic agent, normally used in the treatment of haematological malignancies (Davies and Gilmore, 2003). It inhibits DNA synthesis and is therefore cytostatic and cytotoxic (Ohene-Frempong and Smith-Whitley, 1997). The known and potential side effects are thought to be caused by the drug's interference with rapidly dividing cells (Kennedy et al, 1975; Brawley et al, 2008). Various actual and potential toxicities have been described in the literature; several are expected due to the mechanism of action of the drug. Evidence of other possible adverse effects is emerging but it is still not possible to prove causality, in most cases, due to the paucity of good quality long-term follow-up studies.

Monitoring the incidence and severity of side effects is an essential function of the HU registry. The drug's short and long-term safety profile will determine the feasibility of future usage for SCD patients. A critique of the adverse effects of treatment described in the literature has been undertaken in order to define the parameters that should be monitored by the registry.

3.5.2.1 Bone marrow, kidney, liver and spleen function

HU causes bone marrow suppression and may result in cytopenias therefore patients need regular haematological and clinical monitoring during treatment (Davies and Gilmore,

2003). Myelosuppression is usually dose related and transient. The common toxic effects include a decrease in the patient's white blood cells, neutrophils, platelets, erythrocytes and reticulocytes. Careful regular monitoring of the patient's full blood count (FBC) and clinical wellbeing with appropriate dose adjustments will usually prevent or control these side effects (Davies and Gilmore, 2003). Renal function is monitored routinely for signs of renal toxicity because the drug is excreted through the kidneys and small increases in creatinine are sometimes seen while on treatment (Ohene-Frempong and Smith-Whitley, 1997; Halsey and Roberts, 2003). Special care and reduced dosage is required if used in patients with renal dysfunction (Aliyu et al, 2005). Liver function is also monitored but the rationale behind this is unclear. HU has been reported to cause elevations in liver enzymes but this is also seen in SCD patients not on HU therapy (Ohene-Frempong and Smith-Whitley, 1997). Limited evidence shows that HU can preserve and improve splenic function in some SCD patients (Claster and Vichinsky, 1996; Wang et al, 2001; Santos et al, 2002). However, some subjects have developed hypersplenism and splenic sequestration during treatment and patients with a past history of spleen problems appear to be at increased risk of these complications (Wang et al, 2001; Gulbis et al, 2005; de Montalembert et al, 2006). Due to the high risk of death from acute splenic sequestration crisis careful regular monitoring of spleen size and blood parameters in patients with a prior history of splenic complications is advised (de Montalembert et al, 2006).

3.5.2.2 Cutaneous side effects, gastrointestinal upsets and headache

Cutaneous side effects with therapy are increasingly recognised. Melanonychia (nail hyperpigmentation) and increased skin pigmentation or darkening are commonly reported (Kennedy et al, 1975; de Montalembert et al, 1999; Zimmerman et al, 2004). Incidents of hair loss, skin rash and gastrointestinal upsets have also been reported (Kennedy et al, 1975; Najean and Rain, 1997; de Montalembert et al, 1999) but in the MSH clinical trial these problems were no more frequent in the treatment group than in the placebo arm (Charache et al, 1995). Headaches have rarely been reported as a side effect but if attributed to HU they can be a substantial impediment to treatment. For example in one sickle cell patient HU treatment was stopped because of headaches and this was thought to be the source of non compliance with HU in another (Scott et al, 1996; Kinney et al, 1999; de Montalembert et al, 1999). Therapy does not appear to increase the incidence of leg ulcers in SCD except in patients with a history of previous ulcers (Charache et al, 1995;

Chaine et al, 2001; Mendpara et al, 2004). In contrast an increased incidence of late onset leg ulcers have been reported in patients treated for other diseases (Najean and Rain, 1997; Best et al, 1998).

3.5.2.3 Pregnancy and risk of teratogenicity

The safety of HU therapy during pregnancy remains unclear. Teratogenicity has been shown in experimental animals given very high doses of the drug; between 10 -100 times greater than therapeutic doses (Diav-Citrin et al, 1999; Thauvin-Robinet et al, 2001). The largest case series of 32 pregnancies in 31 women, with various diseases, reported no fetal anomalies ascribed to HU treatment but the incidence of interuterine growth restriction, fetal death in utero and preterm delivery were greater than expected (Thauvin-Robinet et al, 2001). However, causality could not be attributed to drug exposure and may be due to maternal underlying disease because these women suffered from SCD (1 case), chronic myeloid leukaemia (6 cases), chronic myeloid splenomegaly (2 cases) and essential thrombocythaemia (22 cases). Thauvin-Robinet et al (2001) reviewed the published cases of HU exposure in expectant mothers and these authors did not find any reports of infant birth defects. Diav-Citrin et al (1999) suggest that the risk to the human fetus associated with maternal exposure to HU may be overestimated. However, there is no routine follow-up of children exposed to HU in utero, therefore any long-term adverse effects on these children is unknown (Brawley et al, 2008). As a result of the lack of good research evidence it is recommended that pregnancy should be avoided during therapy but drug exposure is not an absolute indication for medical termination (Thauvin-Robinet, 2001; Davies and Gilmore, 2003).

3.5.2.4 Spermatogenesis

Hydroxycarbamide has been reported to impair spermatogenesis in male mice (Evenson and Jost, 1993 cited in Davies and Gilmore, 2003) and recent evidence suggests that it probably reduces sperm counts and motility and alters sperm morphology at therapeutic doses in men with SCD (Grigg, 2007; Berthaut et al, 2008; Lukusa and Vermylen, 2008). Despite this limited evidence, of toxicity, it is suggested that male fertility is conserved and pregnancy and birth outcomes are within the normal range (Berthaut et al, 2008). Nevertheless, uncertainties remain regarding the risk to pregnancy and therefore it is routine practice to advise both male and female patients to stop treatment for at least three

months before they or their partner try to conceive (Davies and Gilmore, 2003; Halsey and Roberts, 2003). Some research supports offering male patients sperm cryopreservation prior to HU treatment to preserve their fertility potential (Berthaut et al, 2008; Lukusa and Vermylen, 2008).

3.5.2.5 Risk of malignancy

There appears to be an increased risk of leukaemia after treatment with HU in patients with essential thrombocythaemia and polycythaemia rubra vera (Najean and Rain, 1997; Sterkers et al, 1998; Finazzi et al, 2000 and 2005). Polycythaemia rubra vera can progress spontaneously to leukaemia and it is thought that the leukemogenic potential of HU is observed only in preleukaemic myeloproliferative syndromes (Najean and Rain, 1997). In contrast a study of patients with cyanotic congenital heart disease on long-term HU reported no cases of malignancy (Triadou et al, 1994 cited in de Montalemant et al, 1997). There is also evidence of an increased risk of skin carcinomas after prolonged use in patients with myeloproliferative disorders (Callot-Mellot et al, 1996; Najean and Rain, 1997; Best and Petitt, 1998).

Leukaemia and other cancers have been reported in sickle cell patients exposed to HU but there is no evidence that the incidence is higher compared with the general population (Schultz and Ware, 2003; Steinberg et al, 2003; Gulbis et al, 2005; Brawley et al, 2008). There is no evidence that patients with sickle cell disease have an increased tendency to develop leukaemia compared with the general population (Davies and Gilmore, 2003). However the risk of malignancy, due to therapy, is a major concern for patients and clinicians and is a recognised barrier to usage (Zumberg et al, 2005; Brawley et al, 2008).

3.5.2.6 Monitoring toxicity and adverse effects in the SCD HU database

Information is collected on adverse events for both routine clinical monitoring purposes and research. Episodes of myelosuppression and liver and kidney function are monitored routinely at every outpatient clinic attendance by appropriate blood tests, recording of clinical history and physical examination of the patient. Date of last menstrual period (LMP) is recorded to assist with managing pregnancy risk. Cutaneous side effects, hair loss, gastrointestinal disturbances and headache have been recorded annually on a separate HU proforma because this information is not systematically collected as part of normal

clinical management. Pregnancies and birth outcomes have also been recorded on the annual HU proforma. Male patients are not offered sperm cryopreservation prior to starting treatment therefore evaluation of spermatogenesis is not possible. Leg ulcer events have been collected as part of the patient's medical history. Episodes of acute splenic sequestration crisis are identified from inpatient admission data, which have been collected for evaluation of clinical outcomes. Information about the patients' past history of malignancy has been documented at start of treatment and collected annually thereafter. The HU protocol for patient monitoring and data collection at CMH is in Appendix I.

3.5.3 Patient cohort and HU dosing schedule

Patients from four centres, treated with HU for severe SCD, were entered in the sickle cell HU registry. Eligibility criteria and treatment schedule were decided by the patients' clinician. The dosing and clinic monitoring schedule are described in Figure 3.6. The dosing schedule was changed, in 2002, from a starting dose of 20mg/kg/day to 15mg/kg/day and increased every four weeks instead of every two weeks. The aim of treatment was to reach a maximum tolerated dose (MTD) or a maximum of 30mg/kg/day whichever is lower. MTD was achieved by increasing the dose until the patient developed haematological toxicity and then reducing the dose by 2.5 mg/kg/day. This lower dose was considered the patient's MTD. Haematological toxicity was defined by absolute neutrophil count (ANC) < 2 x 10^6/ml, platelets < 80 x 10^6/ml, reticulocytes < 1% or 100 x 10^9/l and/or drop of 3g/dl in haemoglobin (Hb) below the patient's baseline value.

Commence HU Dose

Adults & Children – 15 mg/kg/day
Monitor 2 weekly

MTD
Monitor 6-8 weekly

HU Toxicity

NO

Increase HU Dose 4 Weekly
Monitor 2 weekly

YES

Monitor 2 weekly Until Stable

Stop HU

FBC Recovered
Restart @ 2.5 mg/kg/day lower or 500 mg capsule
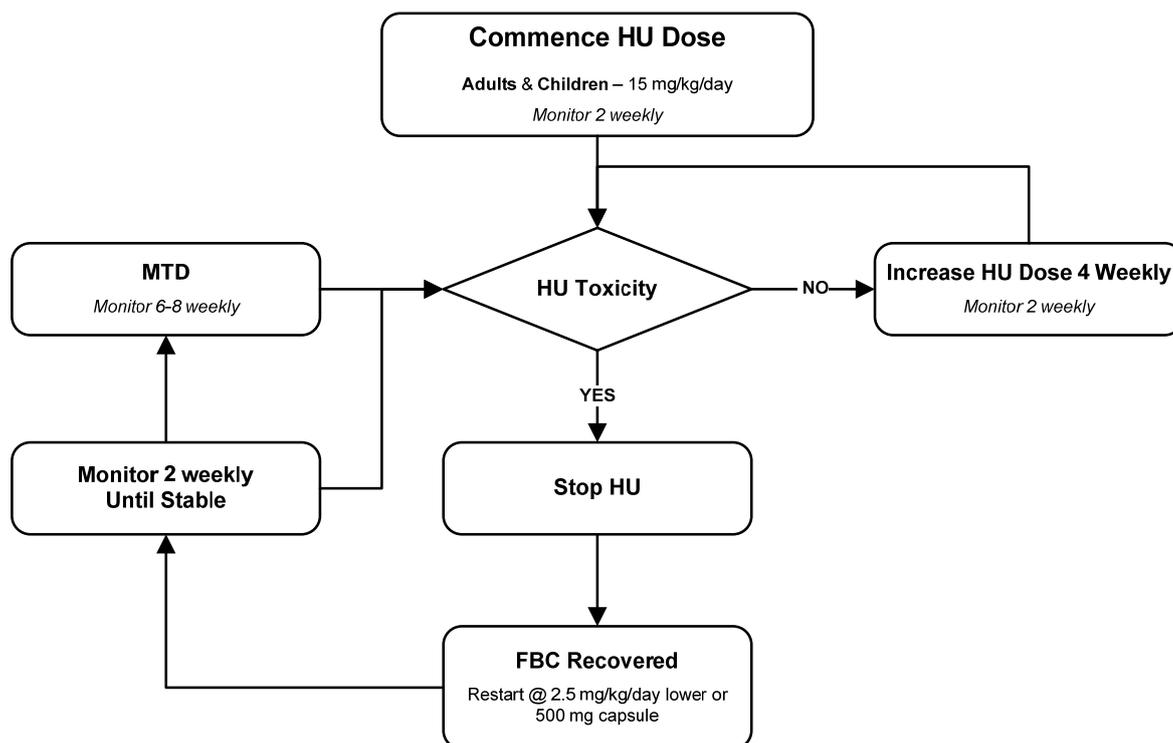
Figure 3.6: Schedule for Monitoring Sickle Cell Disease Patients on Hydroxycarbamide (HU) Treatment

3.5.4 HU data collection methods

Retrospective and prospective clinical and laboratory data were collected on all patients from the start of their treatment. Therefore each patient had a different starting date for data collection. Data was collected on specially developed proformas. A manual with definitions of clinical events was developed to ensure standardization in recording between data collectors (copy shown in Appendix II). A registration form was completed when the patient started HU (Proforma 1) and then a single page follow-up form (Proforma 2) was completed for each outpatient clinic visit thereafter. These proformas captured the clinical and haematological data described in Tables 3.6 and 3.7. The registration form collected clinical data on the patient for the 12 months prior to start of treatment. This provided the baseline patient values for the study. Reason for starting therapy, treatment objective (maximum tolerated dose or set dose) and daily dose given were also collected at registration. An inpatient admission proforma was developed for systematic capture of inpatient admission episodes prior to HU therapy (Proforma 4). The follow up proforma included a question about compliance with treatment and menses (date of last menstrual period). The form was revised in September 2004 and the updated version collected

information about contraceptive use to assist in monitoring the risk of pregnancy during therapy. In addition, a single page annual follow-up form was completed which captured further data on side effects of therapy, vital status of the patient, status of HU treatment, reasons for HU withdrawal, treatment objective (MTD or set dose), history of malignancy, information about pregnancy and birth outcome (Proforma 3). These proformas are included in Appendix III. Patients on HU therapy also had the standard SCD proformas completed at registration and annually, although this data was not analysed as part of this study. These proformas were in use to capture demographic and clinical data for all SCD patients regardless of treatment type.

All the data collection tools could be downloaded from the registry website at www.hbregistry.org.uk. Participants were issued with usernames and passwords to access the members' area. The data collection proformas were introduced in August 2001 and therefore data was entered retrospectively for those patients who commenced HU prior to that date. Data collection was undertaken by the registry co-ordinator at three hospital sites and by the doctors, nurse specialist and registry co-ordinator at the fourth site. The information was double checked by a registry co-ordinator against the medical records for missing or inaccurate data.

3.5.5 Data management

The laboratory and clinical variables were summarised at two monthly intervals for clinical management purposes and annually for research analysis. Patients were expected to be reviewed in clinic at least every two months when their treatment was stable. Therefore two monthly aggregates of data provided a review of the patient in the previous two months.

Annual clinical evaluation included the following: status of patient (alive/dead), treatment status, number of inpatient admissions and days in hospital, inpatient admission diagnosis, number of transfusion events, pregnancies, incidence of serious adverse events and haematological toxicity events, treatment objective (e.g. MTD or set dosing schedule) and whether the latter was achieved, and mean HU dose per kilogram prescribed daily.

Annual blood investigations included total haemoglobin (Hbg/dl), haemoglobin F% (HbF%), mean cell volume (MCV fl), absolute neutrophil count (ANC $x10^9$/l), reticulocytes (retics $x10^9$/l), and serum total bilirubin (umol/L). Other variables were collected to assist with clinical management but are excluded from the analysis. In addition, contraceptive use, menses and data regarding side effects were evaluated at one site.

3.5.6 Statistical methods and analysis

The objective was to compare the changes in variables over time to measure haematological and clinical benefit from treatment. Changes from baseline (yr 0), to each of the yrs 1,2,5,7, and 9 were analysed to identify significant changes associated with HU usage. Baseline year consisted of data collected for the year prior to the patient starting HU and the subsequent data consisted of data collected for the specific year being measured.

The statistical package used for the analysis was Stata, Version 9.0., by StataCorp, Texas, USA. For changes over time, that were normally distributed numerical variables, the paired t-test was used to compare the paired sets of data. The Wilcoxon matched pairs test was used if a variable was not normally distributed and the Fishers Exact for small numbers. The number of subjects in each analysis was reported to aid interpretation of results. For example it was expected that there would be fewer patients on treatment in the long-term therefore the results would be less robust for years 7 and 9 than for the earlier years' analysis, which had larger numbers of patients included.

For normally distributed continuous variables the mean and standard deviation (SD) was calculated at each time point. The mean change over time (and 95% confidence interval) was calculated for the same time point (the mean difference from pre-treatment values to yr 1,2,5,7,9). Finally the statistical significance (p-value) of the change in the value of the variable from baseline to each year assessed was calculated. If variables were not normally distributed the median and inter-quartile range (IQR) at each time point was calculated. The median (and 95% confidence interval) change over time was reported and the p-value indicating the statistical significance of each result was calculated. For categorical variables the numbers and percentages were reported.

The following references refer to Table 3.6 and 3.7. To view the references in full please see the Reference List.

[1] Rodgers et al (1990)
[2] Steinberg et al (1997)
[3] Steinberg and Rodgers (2001)
[4] Rodgers (1997)
[5] Maier-Redelsperger et al (1998)
[6] Powers et al (1984)
[7] Platt et al (1994)
[8] Noguchi et al (1988)
[9] Davies and Gilmore (2003)
[10] Charache (1997)
[11] Charache et al (1992)
[12] Ferster et al (1996)
[13] Aliyu et al (2005)
[14] Maier-Redelsperger et al (1999)
[15] Ohene-Frempong and Smith-Whitley (1997)
[16] Steinberg (1997)
[17] Styles et al (1997)
[18] Zimmerman et al (2004)
[19] Halsey and Roberts (2003)
[20] Kinney et al (1999)
[21] Charache et al (1995)
[22] Gulbis et al (2005)
[23] Hankins et al (2005)

Chapter 4: Utility of a High Quality Sickle Cell Disease Registry/ Clinical Database for Clinical Care and Research

4.1 Introduction

It was hypothesised that registry information would play a dual role in patient benefit with outputs being utilized for direct patient care and audit as well as utilisation of data for research purposes. The geographical coverage and case ascertainment attained is reported in section 4.2.1. Section 4.2.2 describes the contribution of registry information for purchasers and service providers. This thesis utilized the data from the hydroxycarbamide (HU) sub-registry to demonstrate the value of a clinical database for clinical patient management and health service research in sickle cell disease (SCD). Sections 4.2.3 and 4.2.4 provide examples of how registry outputs were used for routine patient management and the final section (4.3) reports the outcomes of long-term HU treatment in a cohort of sickle patients managed in routine clinical care settings.

4.2 Benefits to patients and service providers

The registry provided aggregated data reports to the local Managed Clinical Network (MCN) for haemoglobinopathies to support equitable and effective provision of health services for sickle cell disorder and thalassaemia patients within the local health community. The sickle cell clinical database directly supported clinicians at the point of care provision to improve patient treatment and outcomes. This was achieved by provision of data for local clinical audits and developing individualized patient reports for patient management.

4.2.1. NWL sickle registry: geographical coverage and completeness of case ascertainment

Four of the nine hospitals in the North West London (NWL) Health Sector participated. As stated earlier Northwick Park (NPH) and Central Middlesex (CMH) hospitals amalgamated to form the North West London Hospitals NHS Trust. Sickle cell disorder and thalassaemia patients attending NPH were gradually transferred to CMH and entered into the registry at

the CMH site. Consequently patients from five of the nine hospitals populated the registry over time. Alli (2002) reported 1113 known SCD patients in NWL, of which 872 attended these five hospitals, therefore it was estimated that 78 percent of the total SCD population was covered by the registry.
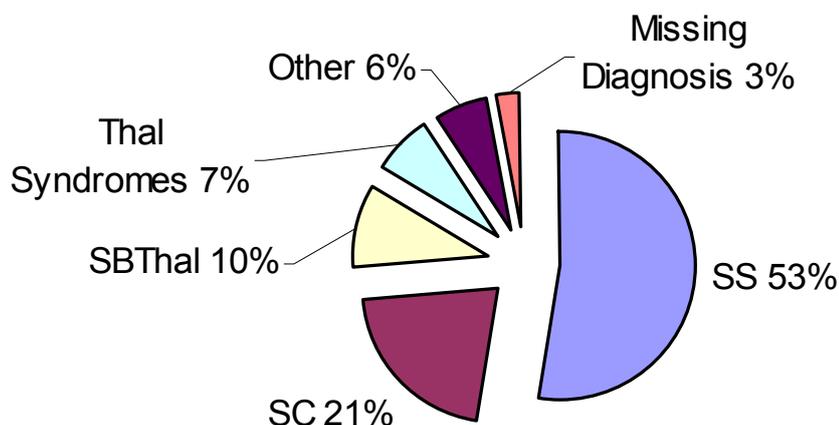
Figure 4.1:CMH, Ealing, Hammersmith, West Middx. Hospitals - 828 Patients by Hb Type

Figure 4.1 shows the number and proportions of patients with clinically significant haemoglobinopathies attending these hospitals. At the 31/03/2004 there were 828 patients identified by the registry of which the vast majority (695 or 84%) suffered with sickle cell disease. The data from Figure 4.1 was compared with the data presented in Table 3.1, Chapter 1, to estimate the effectiveness of case ascertainment. The prevalence figures reported by Alli (2002) were used as the reference. This data suggested that the registry had identified 62 percent (695/1113*100) of the sectors' known SCD population and 89% of those attending the four participating hospitals (695/782*100). If NPH is included than 80 percent (695/872*100) of the potential patients were identified. However, a poorer result was achieved when the population prevalence estimate derived with the Davies et al (2000) method was used for the reference/ gold standard. This method estimated a SCD population of 1468 in NWL (see Table 3.1). Therefore the registry identified 47 percent of potential cases (695/1468*100) by the 31st of March 2004 if this estimate is indeed the true prevalence. Due to funding restrictions only cases from CMH were ascertained after the end of March 2004.

4.2.2 Patient characteristics and implications for service provision

Aggregated anonymised demographic and diagnostic information was collected for all haemoglobinopathy patients attending these hospitals, including those with thalassaemia syndromes. This information provided the core dataset for quantifying prevalence of sickle cell and thalassaemia and mapping local hospital workloads and types of service provision required. Figures 4.1, 4.2, 4.3 and 4.4 describe the diagnostic and demographic profile of haemoglobinopathy patients attending the participating hospitals.
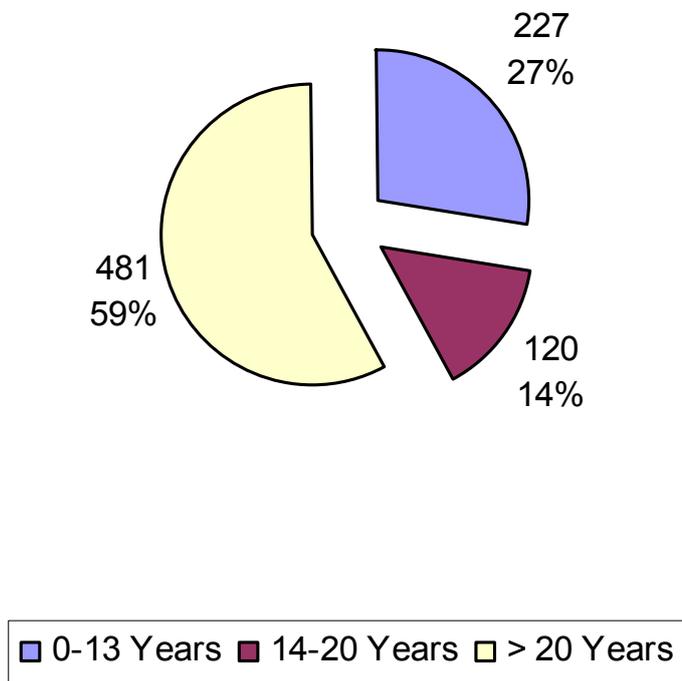
Figure 4.2: Ealing, Hammersmith, West Middx. Hospitals - 828 Patients by Age Group
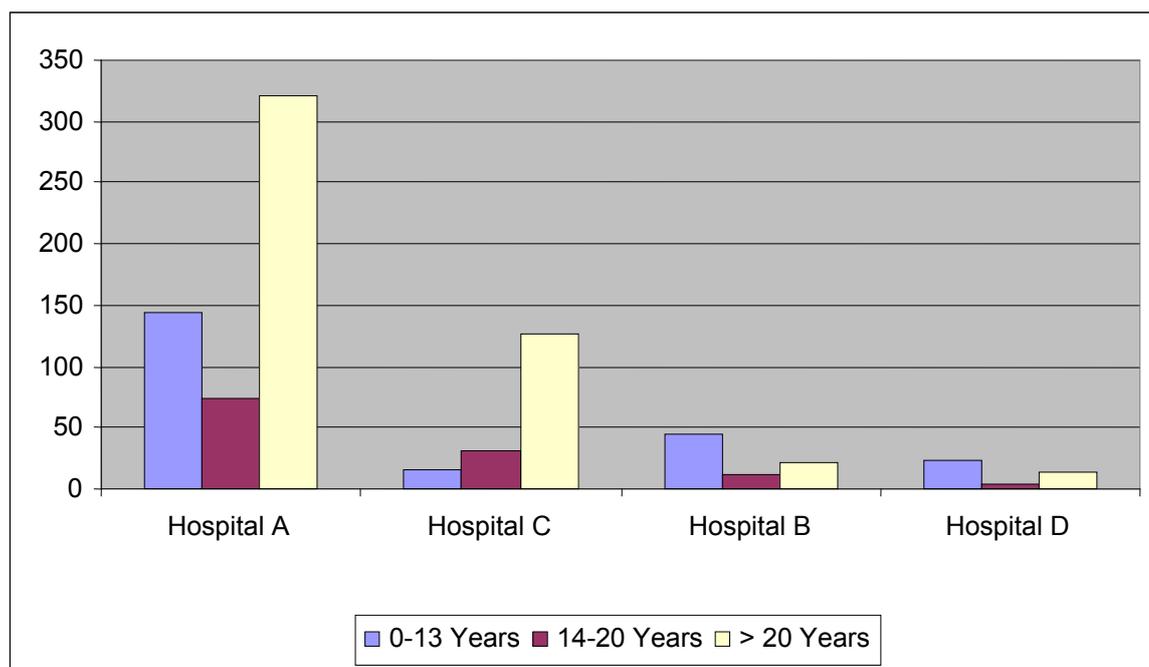
Figure 4.3: CMH, Ealing, Hammersmith, West Middx. Hospitals - 828 Patients by Age Group

While the majority suffered from SCD, as shown in Figure 4.1, there were significant numbers of patients with thalassaemia syndromes. Both conditions have complicated and lifelong health care needs therefore the Primary Care Trusts (PCTs) and MCN required basic demography on both conditions for adequate needs assessment. Figure 4.2 demonstrates that approximately three fifths of all patients were adults and another quarter were teenagers or young adults. A disproportionately high number of adults attended Central Middlesex (CMH) and Hammersmith hospitals (Figure 4.3). Figure 4.4 describes the PCT of residence of patients attending each site. Results suggested that many patients accessed services outside their resident health boundaries. For example the majority of patients resident in Brent and Harrow PCTs attended CMH but half of Ealing patients attended hospitals outside their PCT of residence with especially large numbers attending CMH and Hammersmith Hospital. Furthermore it was evident from Figure 4.4 that CMH and Hammersmith attracted patients from across the whole sector and also large numbers from outside the health district.
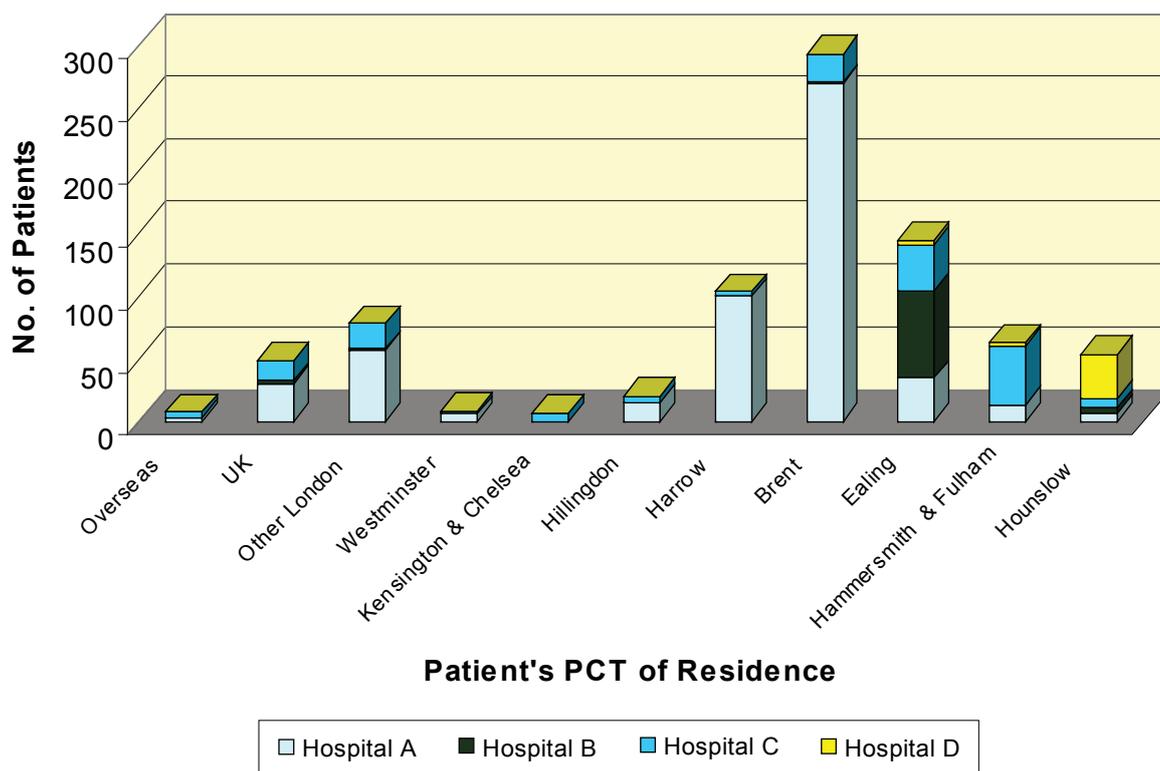
Figure 4.4: CMH, Ealing, Hammersmith, West Middx. Hospitals Haemoglobinopathy Patients (828) by PCT of Residence

Data from the registry was able to provide an assessment of the uptake of HU treatment within participating hospitals. Table 4.1 shows the prevalence of HU use among HbSS adult patients in each hospital and overall at 31/03/2004.

Table 4.1: Proportion of adult HbSS patients on HU therapy on 31/03/2004

Hospital	Total adults with HbSS	No. on HU	% of total on HU
A	164	22	13%
B	14	2	14%
C	77	10	13%
D	5	0	0%
Total	260	34	13%

Adults = ≥ 16 years

These are examples of the data reports that were provided to health professionals, the local PCTs and the North West London (NWL) Haemoglobinopathy MCN to assist with local clinical audits, service planning and management and needs assessment for

haemoglobinopathy patients in the health sector. Table 4.1 demonstrates the utility of the registry for evaluating diffusion of health technologies (HT). This information was presented at the local annual MCN conferences, which were attended by health professionals, purchasers and service users. Written reports were also provided to stakeholders and the presentations were uploaded to the registry website, which could be accessed by health professionals and the public. An example of an annual report is included in Appendix V. Appendix VI is an example of a research manuscript published in a peer review medical journal using patient data from the CMH registry.

4.2.3 Data quality assurance

The registry identified patients to populate the SCD clinical database. Sickle cell disorder patients gave consent for their clinical information to be entered into the database and used for research. The clinical database did not include patients with thalassaemia syndrome or those with non-clinically significant haemoglobin variants, for example HbCC.

Clinical and demographic information was collected at registration and annually thereafter. Patients on HU treatment had additional information gathered as described previously in Chapter 3. The following methods were used to ensure data entry was accurate and complete:

i. Diagnostic criteria; All patients entered into the registry had their diagnosis verified by blood tests. The laboratory tests used for diagnosis were haemoglobin electrophoresis (e.g iso-electric focusing (IEF) or cellulose acetate electrophoresis) and/or high performance liquid chromatography (HPLC). The full blood count (FBC) indices were used to corroborate the result. These tests were conducted in quality assured/ accredited laboratories, as specified in Chapter 1. Where appropriate, making a diagnosis involved additional information including family studies, DNA analysis and evaluation of clinical symptoms.

ii. Data collection tools were developed, as described in Chapter 3, to ensure consistency and reliability of data between sites and data collectors. These tools included the Glossary of SCD study definitions and grading tables, as shown in Appendix II and standardised proformas for data collection across sites (Appendix III).

iii. Collected data was second checked against the patient's medical record by a member of the registry team at one site.

iv. Disagreement between the data elements collected by different data collectors were resolved by arriving at a consensus as to the true value of the variable. The consultant or other experts were consulted to verify the true value of a variable if there was doubt about a data item. For example diagnosing an acute chest syndrome event (ACS) was often difficult. The discharge letter sometimes did not record the event but scrutiny of the inpatient admission notes, chest x-ray results and physiologic data indicated that the patient did suffer an ACS event (using the criteria for diagnosis defined by the Registry).

v. Manual and automated internal consistency checks were implemented. A draft copy of an electronic patient record (EPR) was created for each patient from the inputted data. This record included a summary or the entire patient's data and a log file, which identified missing and inconsistent information. This EPR was sent back to the registry co-ordinator for verification, completion of missing fields and correction of inaccurate data. The database was then updated with the corrected data. This data was then used to produce the patient's EPR and for research and audit purposes.

vi. Other internal consistency checks included visual and automated checking for values outside the normal ranges, for example blood test results. Data elements entered in different parts of the electronic patient record were automatically cross checked for consistency. For example blood transfusion events were checked against the inpatient admission records and the past medical history record. In addition visual inspection of the EPR proved to be an effective and quick method of identifying illogical and/or inconsistent data.

vii. It was not possible to conduct a formal inter-rater and intra-rater reliability study as part of the quality assurance procedures.

4.2.4 Automated patient record for SCD patients

Automated reporting systems produced succinct but comprehensive individualized patient reports for clinical management. A second individualized patient report was developed for the sub-set of patients taking HU therapy (see Appendix IV for a sample of the HU report). These reports were developed in Microsoft Excel and print copies were put in the patients' medical notes for use during outpatient clinic consultations.

This HU report was presented in both tabular and graphical format. Figure 4.5 is an example of the graphical report which formed part of the patient's health record. It summarised key haematological and clinical information essential for monitoring a patient's response to HU. As discussed in Chapter 3 the blood results and clinical data were summarised every two months for clinical management purposes. The annual summary was used to evaluate the patient's clinical progress and for research. For example the HU study conducted as part of this thesis utilized this information; the results are reported in the next section (4.3).
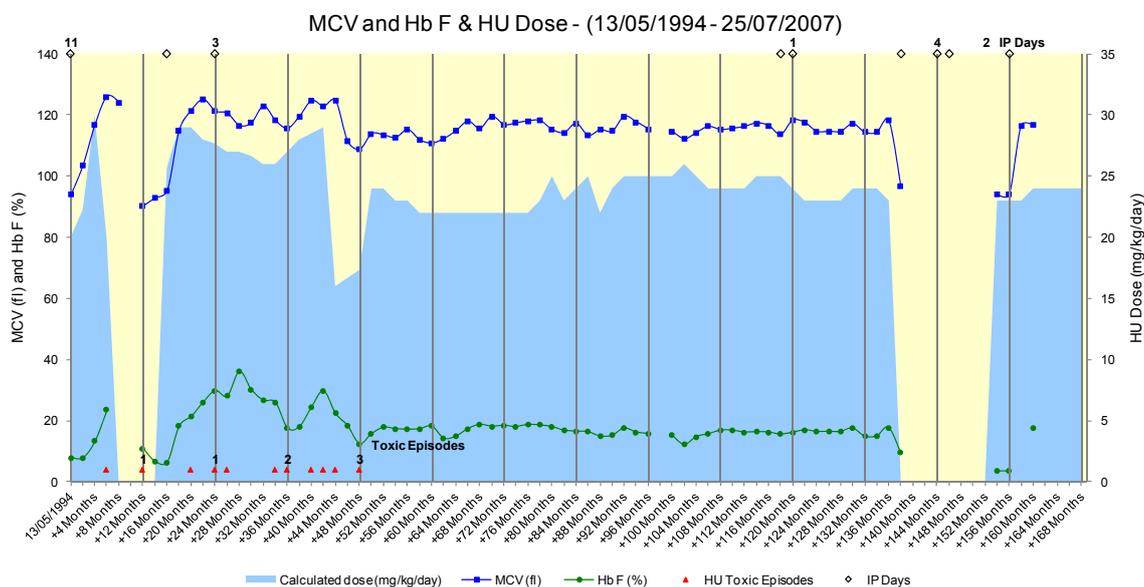
Figure 4.5: Sample Patient Graph

Figure 4.5 reports the patient's mean cell volume (MCV fl) and Hb F% with the daily HU dose from start of treatment (13/05/1994) to the end of follow-up. The right axis is the daily prescribed dose of HU and the patient's actual dose is represented by the shaded area in the graph. This patient stopped treatment twice, as shown by the absence of shading,

after eight months and 136 months. It can be seen from the data that the rise in MCV and HbF% was dependent on the HU dose. The vertical bars delineate each year of treatment. The numbers on the top of the vertical bars represent the annual number of inpatient days. In this example the patient had 11 inpatient days in the baseline year, prior to starting HU, no inpatient days after 12 months and three during the second year of treatment (from 12 to 24 months). The triangles identify when the patient suffered a myelosuppressive episode and the total number of toxic episodes per year were displayed. In this example the patient continued to suffer toxicity until the daily dose was reduced to approximately 24- 25 mg/kg/day after four years.

The HU response graphs provide a succinct visual summary of the patient's journey on treatment. Figure 4.5 is a good example of the value of these graphs in clinical practice. It is now possible to monitor the patient's response to treatment more accurately and rapidly identify when dose changes are required. This graph is also very useful for explaining the benefits and difficulties of HU treatment. In this instance the patient journey to a stable treatment regime took four years. Treatment benefit for this patient is evident from looking at the graph.

4.2.5. Utility of patient record

Patients with complicated disease and care requirements accrued most benefit from the patient reports. They were useful for actively involving the patient in their care and treatment decisions. Specific examples of where the individualized patient reports have proven beneficial to patient care are described.

Case A:

A teenager wanted to stop HU treatment, after six years, because his/her health improved and it was thought that the therapy was no longer required. The HU report was used to discuss with the patient their pattern of clinical and haematological response with treatment adherence compared with non adherence. In this instance the patient's report enabled the doctor to demonstrate that during treatment the severity of their disease was diminished with associated improvement in quality of life, measured by reduction in annual inpatient admission days, pain crisis events and other sickle cell disease complications.

Case B:

It was proving difficult to adequately reduce the frequency and severity of an adult patient's painful crises with HU because chronic medical problems unrelated to SCD compounded and aggravated the patient's sickle cell symptoms. The graphs of HU clinical and haematological response were used to explore, with the patient, the possibility of small incremental dose increases to help symptom relief and at the same time avoid toxicity. It proved possible to increase the daily dose with strict monitoring. In addition the patient had improved understanding and appreciation of the dose limitation due to toxicity.

The main drawback of the patient record was the restricted access due to the limitations of the hospitals IT systems. The reports were kept on a single computer and could be printed and put in the patient's medical notes. Clinicians would have preferred the reports to be held on a central server where they had unlimited direct access to the data and reports. They also wished to be able to make more use of the data to save time and avoid duplication of information. A typical example was the desire to integrate relevant information from the reports into patient correspondence such as outpatient clinic letters to GPs.

4.3 Feasibility and benefit of hydroxycarbamide as a long-term treatment for sickle cell disease patients: experience of the North West London Sickle Cell Disease Clinical Database.

The focus of this study was the cohort of registry patients treated with HU. The aim was to evaluate the long-term feasibility and benefit for SCD patients treated with HU in routine clinical care. Results are presented in sections 4.3.1 to 4.3.7.

4.3.1 Patient and data characteristics

Eighty patients started HU therapy but 18 were excluded. Outcomes were evaluated after a full year on treatment therefore those patients taking HU for less than 1 year were excluded. Likewise if patients stopped using the drug in the early part or middle of a treatment year their data was censored at the end of the last full year on therapy. If nine months or more HU treatment was taken it was considered a full year for analysis purposes. Only patients with the most severe forms of SCD were included to enable

comparison of results with other studies, which have been mainly exclusive to HbSS and HbS/β^0thal phenotypes. Consequently fourteen patients were omitted because they received HU for less than one year and four because they were either HbSC or HBS/β^+thal phenotype. The remaining cohort of 62 patients included 51 adults and 11 children. There were 38 males and 24 females of which 55(89%) were HbSS, six HbS/β^0thal and one SD^{Punjab}. Mean age at start of treatment was 28 years (range, 16-44yrs) for the adults and 10 (range, 1-14) for the children. Thirteen were switched from blood transfusion programmes to HU therapy. Follow-up ranged from 1-13years. Data was censored after nine years because there were too few patients for analysis beyond this time point. This totalled 249 person-years of data with a median follow-up of three years (IQR, 1-6yrs).

Table 4.2 shows the reasons for commencing HU. The majority of patients started treatment for frequent inpatient pain crisis events or pain crises with another sickle complication. The second most common indication of HU was acute chest syndrome (ACS) events or ACS with another medical problem, usually pain crises. Eight patients commenced treatment for other indications including having symptoms in the community which were disruptive to activities of daily living such as frequent school absences. In eight cases it was not known why HU was started.

Table 4.2: Reason for initiating HU therapy

Indication	No. of patients
Recurrent IP pain crisis events	21
IP pain crisis events and ACS	11
IP pain crisis events with additional complication	6
ACS	4
ACS with additional complication	4
Symptomatic in the community	4
Severe anaemia	1
Chronic sickle lung and alloantibodies	1
Chronic chest/sternum pain	1
Alternative to Tx programme (primary reason not known)	1
Not known	8

IP = inpatient, Tx = blood transfusion
The additional complications included 3 with chronic sickle lung (CSL), 2 avascular necrosis, 1 priaprism,1 symptomatic in the community, 1 mesenteric syndrome, 1 salmonella septicaemia and 1 transient ischaemic attacks

4.3.2 Laboratory parameters

The pattern of haematological response is shown in Tables 4.3 and 4.4. For haemoglobin (Hb) there was a statistically significant increase in mean annual value between baseline and each of years 1, 2, 5 and 7 of treatment. The biggest difference was after seven years, where values were, on average, 1.2 g/dl higher than at baseline. There was no difference between years zero and nine, but the number of patients in this analysis was possibly too small to achieve statistical significance as the mean increase was similar to what was attained in earlier years. As expected a statistically significant increase occurred between baseline mean cell volume (MCV) and each subsequent time point measured. The difference from baseline to year one and two was 18 fl which increased to 23 fl after five years. The Hb F percent analyses showed patients achieved statistically significant higher mean annual values for each year on HU compared to pre-therapy, with a mean annual increase of between 9-13 percent approximately. A statistically significant drop in absolute neutrophil count (ANC) was observed between baseline and each subsequent year, with mean values being at least 3×10^9/l lower than baseline. The median annual percentage reticulocyte (retic) count was reduced throughout HU use but the reduction was statistically significant after one and five years only. There was some evidence of a difference for year seven as well, although this result was only of borderline statistical significance (p=0.05). Median annual total bilirubin was statistically significantly decreased from baseline for years 1, 2 and 7 on treatment, with a median reduction of between 10-18 umol/L.

Table 4.3: Clinical and biologic outcomes achieved with HU treatment (a)

Variable	Year	N	Year 0 Mean (SD)	Last Year Mean (SD)	Difference Mean (95% CI)	P-value
Dose	1	62	15.2 (4.9)	18.1 (8.4)	2.9 (0.4, 5.4)	**0.02**
(mg/kg/day)	2	46	15.7 (5.2)	19.3 (8.1)	3.5 (0.7, 6.4)	**0.02**
	5	21	16.5 (4.7)	18.7 (7.5)	2.2 (-1.8, 6.3)	0.26
	7	14	16.7 (4.3)	20.3 (5.6)	3.6 (-1.4, 8.5)	0.14
	9	8	16.5 (2.5)	18.8 (4.9)	2.3 (-1.0, 5.5)	0.14
HB (g/dl)	1	60	9.0 (1.6)	9.7 (1.7)	0.8 (0.4, 1.1)	**<0.001**
	2	42	9.1 (1.6)	9.7 (1.4)	0.7 (0.3, 1.1)	**0.002**
	5	20	9.1 (1.6)	9.9 (1.3)	0.7 (0.2, 1.3)	**0.01**
	7	14	9.1 (1.4)	10.3 (1.3)	1.2 (0.5, 1.8)	**0.002**
	9	8	9.0 (1.3)	9.7 (1.2)	0.7 (-0.7, 2.0)	0.28
MCV (fl)	1	60	86 (10)	104 (17)	18 (14, 21)	**<0.001**
	2	41	86 (10)	104 (18)	18 (14, 21)	**<0.001**
	5	20	91 (8)	113 (13)	23 (18, 27)	**<0.001**
	7	14	93 (8)	115 (16)	22 (15, 29)	**<0.001**
	9	8	95 (8)	116 (14)	20 (13, 28)	**<0.001**
HB F%	1	59	5.9 (5.0)	18.7 (11.6)	12.8 (10.2, 15.4)	**<0.001**
	2	42	6.2 (4.8)	18.3 (11.0)	12.2 (9.3, 15.1)	**<0.001**
	5	19	5.4 (4.4)	17.8 (9.4)	12.4 (8.7, 16.2)	**<0.001**
	7	13	5.9 (4.9)	18.8 (9.1)	12.9 (8.7, 17.1)	**<0.001**
	9	8	7.1 (4.3)	16.3 (6.5)	9.2 (5.0, 13.4)	**0.001**
ANC (10⁹/l)	1	55	7.4 (3.4)	4.4 (2.2)	-3.0 (-4.1, -1.9)	**<0.001**
	2	39	7.5 (3.2)	4.5 (2.2)	-3.0 (-4.3, -1.7)	**<0.001**
	5	20	8.4 (3.5)	4.6 (1.7)	-3.8 (5.7, -1.9)	**<0.001**
	7	14	8.5 (3.3)	4.4 (1.9)	-4.1 (-6.6, -1.7)	**0.003**
	9	8	8.5 (3.5)	4.9 (2.4)	-3.6 (-6.8, -0.4)	**0.03**
Pain crisis	1	43	2.05 (2.56)	1.33 (1.82)	-0.72 (-1.20, -0.24)	**0.004**
(IP events)	2	31	1.90 (2.07)	1.03 (1.72)	-0.87 (-1.60, -0.15)	**0.02**
	5	17	1.18 (1.38)	0.59 (1.28)	-0.59 (-1.60, 0.42)	0.24
	7	13	1.23 (1.54)	1.00 (1.78)	-0.23 (-1.83, 1.37)	0.76
	9	8	1.13 (1.55)	0.63 (1.06)	-0.50 (-2.34, 1.34)	0.54

The data is paired therefore for a subject to be included in the analysis, values are required at both time points. Consequently, there are a different number of subjects in each of the analyses. (The figures reported are the number of subjects on which the analysis was based, the mean (standard deviation) at each time, along with the mean (95% confidence interval) change over time, and p-value indicating the significance of each result.

Abbreviations: IP = inpatient, ANC = absolute neutrophil count

Table 4.4: Clinical and biologic outcomes achieved with HU treatment (b)

Variable	Year	N	Year 0 Median (IQR)	Last Year Median (IQR)	Difference Median (95% CI)	P-value
Retics%	1	37	9.2 (5.3, 136)	6.3 (4.6, 9.5)	-2.2 (-2.0, -0.2)	**0.04**
	2	23	9.3 (5.6, 13.7)	7.5 (5.6, 9.9)	-2.2 (-4.3, 1.2)	0.25
	5	10	13.5 (8.0, 18.1)	7.0 (3.5, 10.7)	-8.5 (-10.3, -0.1)	**0.01**
	7	9	13.0 (5.3, 17.2)	7.1 (4.4, 8.1)	-7.9 (-10.8, 1.0)	0.05
	9	5	17.4 (4.1, 29.5)	6.5 (5.6, 8.9)	-11.2 (-21.7, 3.0)	0.22
Total Bilirubin (umol/L)	1	59	41 (23, 82)	30 (20, 46)	-10 (-22, -8)	**<0.001**
	2	43	41 (24, 89)	29 (20, 49)	-10 (-22, -5)	**<0.001**
	5	19	59 (30, 89)	36 (28, 73)	-10 (-31, 4)	0.08
	7	14	59 (30, 80)	38 (31, 58)	-18 (-38, 8)	**0.04**
	9	8	47 (29, 68)	32 (29, 49)	-15 (-47, 11)	0.12
IP Days (annual no.)	1	46	18 (9, 33)	8 (0, 22)	-8 (-14, -5)	**<0.001**
	2	31	14 (7, 29)	0 (0, 8)	-10 (-21, -6)	**<0.001**
	5	17	12 (7, 32)	2 (0, 12)	-10 (-17, 2)	**0.02**
	7	13	11 (4, 32)	0 (0, 14)	-10 (-25, 0)	**0.01**
	9	8	10 (0, 33)	0 (0, 15)	-5 (-50, 37)	0.62
Chest Syndrome (IP events)	1	43	1 (0, 2)	0 (0, 0)	-1 (-1, 0)	**<0.001**
	2	31	0 (0, 2)	0 (0, 0)	0 (-1, 0)	**<0.001**
	5	17	1 (0, 2)	0 (0, 0)	-1 (-2, 0)	**0.009**
	7	13	1 (0, 2)	0 (0, 0)	-1 (-2, 0)	**0.009**
	9	8	1 (0, 2)	0 (0, 0)	-1 (-3, 0)	**0.03**
Blood Transfusion (events)	1	51	2 (0, 7)	0 (0, 1)	-2 (-6, 0)	**<0.001**
	2	36	2 (0, 12)	0 (0, 0)	-2 (-5, -1)	**<0.001**
	5	18	3 (1, 12)	0 (0, 1)	-3 (-8, 0)	**0.001**
	7	13	2 (1, 12)	0 (0, 0)	-2 (-12, 0)	**0.008**
	9	8	5 (0, 12)	0 (0, 0)	-5 (-12, 0)	**0.03**

Analysis examined the change from baseline (year 0) for those variables that were measured on a continuous scale, but where the distribution of the changes over time was not found to be normally distributed. The figures reported are the median (inter-quartile range) at each time, along with the median (95% confidence interval) change over time, and p-value indicating the significance of each result.

4.3.3 Clinical response

A summary of the clinical findings are reported in Tables 4.3 and 4.4. The mean annual number of inpatient (IP) pain crisis events per patient decreased significantly from pre-treatment for the first two years with a 35 percent reduction after one year and 46 percent after two years. A reduction in mean annual pain crisis events was observed thereafter but it was not statistically significant. Median number of annual IP days was statistically significantly reduced compared to pre-treatment throughout the follow-up period except after nine years. The absolute reduction is striking with the median ranging from 0- 2 days

per annum after two years on HU from a median of 18 days per annum before treatment. The median number of annual ACS events and transfusion events decreased significantly from pre-treatment levels for each year analysed.

To further assess the long-term clinical effectiveness of HU, for this cohort of patients, the adverse event rates per 100 patient-years of follow-up were computed. Number of inpatient admissions was 124.5 per 100 patient-years, number of inpatient days was 1108 and the pain crisis rate was 98. The pain crisis rate for patients with two or more inpatient admissions per year was 25 per 100 patient-years. The rate of ACS events and transfusion events was 9.6 and 50.6 per 100 patient-years respectively.

4.3.4 Serious adverse events

The death rate was 0.8 and the stroke rate was 1.2 per 100 patient-years. Two patients died during follow-up, one 39 year old female after four years treatment and a young man of 20 after three and a half years. The female patient died from a subarachnoid haemorrhage; she had a history of deep venous thrombosis and was on long-term anticoagulant therapy. The 20 year old male patient was admitted with an ACS and rapidly deteriorated with multi-organ failure. He was non compliant with his outpatient appointments and HU regime. Two other patients had infarctive strokes, one after three and a half years and the other after eight years on HU. They were subsequently switched to long-term transfusion programmes. No patient developed cancer during the follow up period but two patients were diagnosed with cancer after data collection ceased. Causality could not be attributed to HU treatment in one case where the patients' medical and social history was likely contributory factors in the development of cancer. This patient, with a history of long-term alcohol misuse, chronic depression and severe hepatic iron overload from previous blood transfusions, developed primary liver cancer (hepatocellar carcinoma) after 11 years on HU. The other patient developed thyroid cancer (papillary cell carcinoma), after 27 months therapy, which was effectively treated. This patient had complained of a lump in her thyroid three weeks after starting HU and two months later a fine needle aspirate was reported as benign.

4.3.5 Toxicities

4.3.5.1 Myelosuppression and cutaneous side effects

The aim of treatment, for the majority of patients, was maximum tolerated dose (MTD) which was calculated by inducing haematological toxicity. Therefore, it was expected that patients would experience dose-dependent myelosuppression on at least one occasion. Overall there were 174 episodes of transient toxicity, yielding a rate of 70 per 100/patient years.

There was no increase or decrease in the incidence of leg ulcers with HU but the overall occurrence was very small. Four patients out of 59 suffered leg ulcers prior to treatment and three of these patients suffered leg ulcer events while on HU. Two patients with recurrent ulcers were found to have deep venous incompetency/ insufficiency. There was no information about venous circulation on the other patients who developed ulceration.

Annual surveys, at one site, revealed that approximately 50 percent of patients experienced mild or moderate melanonychia; two had nail pigmentation prior to therapy. Skin hyperpigmentation occurred in between 5-20 percent of patients. None stopped treatment as a consequence of these side effects. Another patient experienced severe hair thinning and melanonychia after six months while on 34mg/kg/day. The dose was then reduced to 26 mg/kg/day but the toxicities were still present at 12 months and subsequently the patient stopped therapy at 15 months. It is not known why the patient stopped but it is likely that the side effects influenced the decision. There was no statistically significant change in the incidence of nausea and vomiting, headaches or hair thinning compared with pre HU status.

4.3.5.2 Pregnancy and birth outcomes

There were eight pregnancies reported. Five pregnancies occurred in four patients while on HU. Treatment was stopped early in the first trimester when it was known they were pregnant. Pregnancy outcomes included two terminations, one miscarriage and two normal live births. These pregnancies happened despite pre treatment counselling advice to stop the drug three months prior to patient/partner conception. Two patients stopped HU pre conception which resulted in three normal live births. Another pregnant lady was excluded

from the analysis because treatment was stopped after three months due to pregnancy; the outcome of this conception is unknown.

4.3.5.3 Monitoring pregnancy risk

The questions 'date of last LMP (last menstrual period)' and 'contraception use' (no, yes, not applicable) were added to the clinic follow-up questionnaire to help monitor risk of pregnancy. To assess the utility of these questions their completion rate was analysed at one site where the questionnaire was completed prospectively during clinic visits. The question 'date of LMP' was analysed from 1st January 2003 to 31st August 2007 for 12 menstruating adult females ($\geq$ 16 yrs). In 210 proformas the question was only completed on 19.5 percent of occasions. The completion rate for the 'contraception' question, which was introduced later, was analysed for the same site from 1st January 2006 to 31st August 2007. It was completed in 33 percent of the proformas (55 of 82) for 11 adult females but only in 8.5 percent (13 of 153) for the 17 adult males on HU.

4.3.6 Treatment regime

Results of mean daily dose changes from start of treatment (year 0) to year 1,2,5,7 and 9 are shown in Table 4.3. There was a statistically significant increase in dose from baseline for the first two years of therapy only, with a mean increase of 2.9 (CI 0.4, 5.4) mg/kg/day after one year and 3.5 (CI 0.7, 6.4) after two years. The highest mean daily dose reached was 20.3mg/kg/day and the dose varied little throughout the whole follow-up period, from 18.1(SD 8.4) to 20.3 (SD 5.6) mg/kg/day.

4.3.6.1 Attainment of MTD

The goal of treatment was MTD for 91 percent of patients and it was achieved in 65 percent of the cohort. The mean MTD was 20mg/kg/day (SD 4) which took a median time of nine months to achieve (IQR 5-18 mths). Achieving MTD was not straightforward and a variety of barriers were identified. In half of cases where MTD was not attained the problem was non compliance with the monitoring regime and/or the drug. In a further three cases there was insufficient opportunity to achieve MTD as these patients stopped therapy or continued to be frequently admitted to hospital and in receipt of transfusions. In two patients the dose was reduced by the doctor, because of an increase in Hb above 12g/dL

causing viscosity symptoms, and in another patient due to non compliance with outpatient department clinic visits. One patient chose to reduce the dose from MTD and in three patients it was not known why MTD was not established.

4.3.6.2 Techniques for measuring drug non adherence

Non compliance with monitoring regime was evaluated by counting the proportion of outpatient department (opd) visits the patient attended as compared with the number of scheduled opd visits. Non compliance with HU was assessed by a triangulation of information sources. These included the proportion of non attendance at scheduled opd visits and time period between each visit attended, comments about compliance in the free text portion of the follow-up proforma and from the answers to the question about non compliance on the proforma (average number of doses missed per week). As stated in Chapter 3 a patient was prescribed sufficient HU to cover the period between opd visits. Consequently if a patient missed a visit they would run out of their medication or, if not, they were not taking the full amount prescribed on a daily or weekly basis. The question about non compliance was completed at one centre only where the proforma was completed prospectively during clinic. In the other centres the proformas were completed retrospectively from the patient's medical notes by the researcher. This question is not routinely asked during clinic consultations therefore it was invariably incomplete at these sites. Occasionally there were comments in the medical notes addressing the patient's drug adherence, if the clinician was concerned about usage. These were ad hoc entries and not a good source for drug compliance information. In addition the electronic patient record, generated by the registry, was reviewed for evidence of non compliance. For example the trends and changes in MCV and HbF data were inspected to help verify drug usage over time.

4.3.6.3 Maintenance on MTD

Most patients (83 percent) were maintained at their MTD. Two patients became intolerant to their original MTD after four and five years of treatment respectively. In one patient the MTD reduced from 23mg/kg/day to 17mg/kg/day after four years and he was maintained on this dose thereafter. In the other case the patient became progressively anaemic on an MTD of 14mg/kg/day after five years and therapy was switched to monthly transfusions. The dose was reduced in one patient following an aplastic crisis event and another patient's

dose was not increased after weight gain. One patient appeared to have dose reduction for leg ulceration and eventual cessation of therapy. In another case it was probable that there was insufficient opportunity to retain MTD as this patient continued to be admitted to two different hospitals for pain crises which frequently resulted in administration of blood transfusion and cessation of HU during the inpatient episodes. Of note one child, aged 13 months at start of therapy, appeared to become more tolerant to HU with the MTD rising from 16mg/kg/day to 23/24mg/kg/day after two years. This patient's drug adherence was judged as satisfactory by the clinicians.

4.3.7 Patient attrition

Twenty-three patients stopped the drug, 20 continued with treatment and were still being followed up at the end of the study. The remaining 19 patients were on HU but follow-up ceased for reasons outside the control of the registry such as relocation or care transferred to another hospital (5), did not turn up for appointments and were lost to follow-up (6) and funding for data collection ended in three of the hospitals (8).

Eleven stopped treatment indefinitely for medical reasons, as shown in Table 4.5, seven refused HU and it was not known why the other five stopped the drug. The two patients who accrued no clinical benefit were on very low doses due to their susceptibility to myelosuppression. One patient had continual dose reduction for persistent neutropenia to the point that it was of no therapeutic value so treatment was stopped. The other patient had renal dysfunction and was started on a low dose to arrest anaemia, but it proved ineffective.

Table 4.5: Reasons for stopping HU in 23 patients with sickle cell disease

Reason	N	HU treatment (months)	Treatment Post HU*
Infarctive stroke	2	42, 96	Tx programme (2)
Haemorragic stroke	1	44	Died
Progressive anaemia	1	80	Tx programme
Opiod addiction	1	12	Drug rehabilitation + Tx programme
No clinical benefit	2	13, 50	No active treatment (2)
Father child	1	90	Tx programme
Pregnancy (never restarted HU)	3	12, 32, 40	No active treatment (2), Tx programme (1)
Patient refused	7	11, 12, 24, 24, 43, 84,106	No active treatment (7)
Not known	5	12, 15, 24, 24, 36	Not known

Abbreviations: Tx = Transfusion (of blood)
*Numbers in brackets = number of patients

Chapter 5: Discussion, Conclusions and Recommendations

This is the first British study to assess the use of hydroxycarbamide (HU) therapy for sickle cell disease (SCD) patients. Our findings support the results of previous studies that long-term HU is a feasible treatment option and associated with continual haematological and some clinical benefit for SCD patients.

5.1 Improvement in blood indices

Throughout follow-up there remained significant improvements in Hb, HbF%, MCV and absolute neutrophil count (ANC $x10^9$/L) from pre-treatment levels. After nine years of treatment the increase in mean Hb, from baseline, was not statistically significant and the improvement in mean ANC was less significant than in previous years, although the lack of significance is possibly due to the meagre number of participants analysed at this time point. Therefore there was no evidence of bone marrow exhaustion in patients after prolonged HU use. Haemolysis improved with evidence from a sustained absolute reduction in total bilirubin levels, even though the decrease was only statistically significant for the first two years and after seven years was weakly significant. There was also a sustained reduction in annual median reticulocyte counts which was statistically significant after one and five years treatment but this variable had fewer observations in later years, and therefore less power to detect a difference. Overall the haematological outcomes from the present study agree with other research findings. There were substantial and sustained improvement in the blood parameters of SCD patients treated with long-term HU therapy.

5.2 Clinical effectiveness of treatment

Clinically, patients derived benefit for as long as they were receiving therapy but the magnitude of the benefit, for some clinical outcomes, appeared to reduce over time. There was a statistically significant reduction in median annual number of hospital admission days, acute chest syndrome (ACS) events and blood transfusions. The mean number of inpatient (IP) pain crisis events nearly halved during the follow-up, except after seven

years, but this reduction was only highly statistically significant for the first year with some evidence of a reduction after two years (p= 0.02). Therefore the evidence is weak, in this study, for the long-term effectiveness of HU in reducing IP pain crisis events beyond two years of treatment. The reduction in inpatient days was highly statistically significant for the first two years of treatment and remained significant up to seven years (p = 0.02 after 5 years and p = 0.01 after 7 years). There was also a sustained highly statistically significant reduction in median annual ACS events and blood transfusion events up to seven years of treatment.

The number of patients in the clinical analysis at five years and above was less than 20 and this may have been too few for robust results. It will be necessary to reanalyse the data when there are more patients, with longer follow-up, to assess the long-term effectiveness of HU in reducing IP pain crisis events and number of days in hospital in routine clinical practice.

5.2.1 Comparison of clinical event rates with other studies

The adverse event rates per 100 person years for this study, the Belgium registry, the MSH follow-up study and the HUSOFT extension study are presented in Table 5.1 (Steinberg et al 2003; Gulbis et al 2005; Hankins et al 2005). The event rates, reported by Telfer and colleagues (2007), of an untreated cohort of children and young adults are also presented for comparison. Comparability of the studies is limited due to the differing age of the patients in each cohort, the difference in number of patient years of follow-up and the different methods of follow-up.

The Belgian registry had some similarities with this NWL study because patients in both cohorts were treated with HU in routine clinical practice (Gulbis et al, 2005). Also both cohorts only included patients with severe SCD. This study and the Belgium registry had similar event rates per 100 patient-years for IP admissions, IP admission days and IP pain crises, for patients with two or more pain crises per year. The large difference between the annual rate of IP pain crisis events per 100 person years and the rate for patients with two or more crises per year was due to a small proportion of patients who continued to be admitted frequently with pain. This minority of patients accounted for most of the IP admission crisis rate.

The difference in event rates for transient haematologic toxicity can be explained by the differing treatment regimes for each cohort. In contrast to the NWL cohort there was no attempt to push patients to maximum tolerated dose (MTD) in the Belgian registry and consequently patients were not expected to become toxic, on prescribed doses. However differences may also be due to differences in methods of data collection. The Belgian registry collected data annually and therefore some variables are likely to be underreported (Gulbis et al, 2005). The data in the present study was subject to more rigorous data collection methods. Patients' clinical and haematological data were collected at each clinic visit for entry into the NWL sickle database. A query developed by the Registry's computer program identified episodes of haematological toxicity, as defined by the criteria for toxicity in the HU protocol. These criteria are explained in chapter 3, section 3.5.3 and Appendix 1. Therefore toxic episodes were automatically calculated and it is likely that this information is more complete, in the present study, than that collected by the Belgian registry.

Table 5.1: Comparison of cumulative event rates -per 100 person years on HU therapy vs patients not on HU

	This study (NWL registry)	Gulbis et al (2005) (Belgian registry)	Steinberg et al (2003) (MSH follow-up study)	Hankins et al (2005) (HUSOFT extension)	Telfer et al (2007)*** (East London cohort)
Total no. patients	62	109	299	21	≈ < 180
Patient-years of follow-up	249	426	2264	106.4	1456
Mean follow-up (yrs)	3*	3.9	7.6**	4.9	
Median Age (yrs)	10 - children 28 - adults	6	Adults	3.4	≈ 7.4
Events					
IP adm, no.	124.5	138			
IP adm, days	1108	1033			
IP pain crises	98			33.8	63.9
IP pain crises ≥ 2/yr	25	22			
ACS	9.6	3.3		7.5	17.1
Blood Tx events	50.6				
Transient haematologic toxicity	70	1.4			
CVA	1.2	1.3	0.6		0.3
Malignancy	0	0.23	0.1		
Death	0.8	0.23	3.3	0.94	0.1 and 0.27****

Abbreviations: IP adm = inpatient admission, Tx = transfusion, ACS = acute chest syndrome, CVA = cerebrovascular accident
Median age at start of treatment reported
* Median reported
** Mean length of follow-up, includes time on and off HU
*** 180 with HbSS in cohort but those > 16 yrs were excluded from the event rate analysis. Patient years on Hu and blood Tx therapy were also excluded.
**** The death rate was 0.1 if the two infants with HbSS that never attended clinic are excluded from the cohort

The inpatient pain crisis rates per hundred person years varied across all studies, measuring this outcome, in Table 5.1. This may be due to the difference in disease severity of the cohorts. All patients in the present study had severe SCD (because this was the criterion for commencing HU). In contrast the East London cohort excluded patients on HU or transfusion programmes, from the event rate calculations, therefore the most severe patients with SCD were excluded (Telfer et al, 2007). Similarly the patients in the original HUSOFT study were an unselected group chosen to commence HU therefore that cohort would be expected to include patients with a broad spectrum of disease severity, from mild to severe disease (Wang et al, 2001; Hankins et al, 2005). Comparison of the East London cohort and the HUSOFT patients shows that the pain crisis event rate was less in the group of patients taking HU treatment. Disparity between the studies' patient selection criteria prohibit any conclusions being drawn about the differences between the NWL cohort's pain crisis rates and the other studies measuring this outcome.

Table 5.1 also shows that the ACS rate was lower in all studies, including the NWL cohort, compared with the East London cohort (Telfer et al, 2007). Indeed most studies have shown statistically significant reductions in numbers of ACS events for patients treated with HU (Charache et al, 1995; Maier-Redelsperger et al, 1999; Halsey and Roberts, 2003; Gulbis et al, 2005; Hankins et al, 2005).

None of the patients, in the present study, suffered a severe adverse event that could be directly attributed to HU treatment. The rates of serious adverse events, for different patient cohorts, are shown in Table 5.1. These are useful for guidance on the magnitude of serious event rates for SCD patients managed with and without HU therapy. Again due to variation between the studies, in terms of patient selection criteria, it is not possible to compare serious adverse event rates. Patient characteristics that influence the risk of serious events, such as age and disease severity, are dissimilar in each cohort (Platt et al, 1994; Ohene-Frempong et al, 1998).

5.3 Cutaneous side effects

Similar to other cohorts a proportion of patients experienced dermatological side effects including nail darkening and skin hyper pigmentation (de Montalembert et al, 1999;

Zimmerman et al, 2004; Brawley et al, 2008). Such side effects were acceptable to patients and did not warrant cessation of therapy. This study did not find any increase (or decrease) in the incidence of leg ulcers but the overall occurrence was small. A recent systematic literature review reported that HU does not affect the development of leg ulcers in SCD patients, although it is associated with increased incidence when used for patients with other illnesses (Lanzkron et al, 2008). Three of the four patients, in this cohort, with leg ulcers pre treatment developed ulcers while on therapy. Ulcers in SCD patients tend to recur and therefore it is likely that these patients would have developed ulcers irrespective of HU. Case series reports by Chaine et al (2001) and Mendpara et al (2004) found that the majority of the SCD patients who developed leg ulcers while on HU had a history of leg ulcers pre treatment. Does this evidence suggest that SCD patients with previous ulceration may be at greater risk of developing ulcers during treatment or that HU does not confer any protection against recurrence of leg ulcers in this group?

5.4 Pregnancy outcomes

The two patients who completed their pregnancies delivered healthy babies despite taking HU into the first trimester. Other studies have reported the birth of healthy newborns to women who conceive while on treatment (Charache et al, 1995; Thauvin-Robinet et al, 2001; Gulbis et al, 2005). However, there is little data about the safety of HU at therapeutic doses in pregnant women (Thauvin-Robinet et al, 2001). Uncertainty about birth outcomes is a barrier to use and requires further investigation (Lanzkon et al, 2008). The literature is based on case series evidence and data from a few experimental studies, on rats and mice; therefore it is not known whether the incidence of adverse birth outcomes is higher than expected for the populations under study (Lanzkon et al, 2008). For instance in the largest case series of human exposure during pregnancy, by Trauvin-Robinet et al (2001), it was not possible to identify whether the adverse birth outcomes reported were due to maternal underlying disease or exposure to HU.

In addition, the long-term effects on children exposed in utero are not known (Brawley et al, 2008). Research studies to date have not systematically followed-up the offspring of patients with SCD, after birth, to evaluate developmental abnormalities over time. Most cohort studies, including this sickle cell database, only report birth outcomes. If it is not

possible to follow-up every outcome of interest then targeted studies can be conducted using representative samples of patients identified by registry data. This strategy was used by the EUROCARE researchers, as discussed in Chapter 2. They conducted high resolution studies to investigate the causes of poor cancer outcomes in geographical areas or in groups of patients identified with comparatively inferior outcomes.

5.5 Incidence of pregnancy on HU

It is standard practice to advise patients to avoid conception while on HU treatment (de Montalembert et al, 1999; Davies and Gilmore, 2003; Gulbis et al, 2005). Patients entered in the present study were counselled, pre therapy, to avoid pregnancy. Should they decide to have a child, during treatment, the clinical management options were discussed. Despite these measures four patients conceived while on therapy. Unplanned pregnancies continue to be reported during HU exposure, not only in women with SCD but also in those treated for other conditions (Charache et al, 1995; Thauvin-Robinet et al, 2001; Gulbis et al 2005; de Montalembert et al, 2006). There is some evidence that up to 50 percent of pregnancies are unplanned therefore it is possible that some may result in unintentional fetal drug exposure (Skrabanek, 1992; Diav-Citrin, 1999).

5.5.1 Strategies to reduce pregnancy risk

In this study asking patients about contraception use and documenting date of last menstrual period (LMP) at each visit was not a successful strategy for monitoring pregnancy risk. Despite the use of a standardised proforma, data on these specific variables were often missing in the database. The proforma was checked against the patient's medical record for accuracy and completion of missing data. Some doctors completed the proforma retrospectively, after clinic, or they were completed by the researcher retrospectively. If the information was not documented in the medical notes it could not be completed, and was missing in the database. Therefore the reason for missing information, in the database, for these variables was insufficient clinical documentation in the patient notes to complete the questions. The literature review, in Chapter 2, identified this problem as a major source of incompleteness and inaccuracy in registry data. Reported strategies to improve the data source include a standardised proforma for clinical data collection but if

the questions are not routinely asked during clinical consultations this may not help reduce missing data. This would appear to be the problem with these variables. Menstrual cycle and contraceptive use is not regularly documented in SCD patients' clinical notes. In addition this information may have been seen as sensitive and some doctors might have been uncomfortable with this line of questioning or felt it was unnecessary. This information should be routinely asked at clinical consultations. Perhaps there is a need for the clinical staff to be better informed of the importance of asking these questions.

5.5.2 Counselling and monitoring strategies

Monitoring pregnancy risk is very important for patients taking HU. It is known that concerns about lack of vigilance with contraception is a substantial barrier to prescribing HU and interventions have not been tested to minimize pregnancy risk (Zumberg et al, 2005). Unfortunately the experience from this study and that of other investigators suggests that reproductive counselling, at the outset of treatment, is not a totally effective strategy. Platt (2008) advises doctors to conduct systematic counselling sessions throughout the duration of HU use.

Prescribing and monitoring HU has traditionally been the domain of the hospital doctor but it might be beneficial to enlist the help of other healthcare professionals. Haemoglobinopathy nurse specialists and counsellors could educate patients about HU risks and undertake surveillance of contraceptive use and adherence during therapy. Patients and parent/carers build up long-term supportive relationships with these practitioners (Gould et al, 2000; De, 2005). Likewise GPs could play a more active role in monitoring patients on therapy via shared care protocols. Most sickle cell patients already benefit from being cared for by multidisciplinary care teams. Therefore, the infrastructure is already in place for improving communications and links with other primary care health professionals. Indeed strengthening the primary and secondary care team approach is strongly advocated in the recent national guidelines for caring for children and adults with SCD (NHS Sickle Cell and Thalassaemia Screening Programme, 2006b; Sickle Cell Society, 2008).

5.6 Therapeutic dose and dosing schedule

Mean daily dose was statistically significantly increased from start of treatment for the first two years only (p= 0.02). There was no significant change from baseline thereafter. Of note the mean daily dose remained modest at between 18.1 (SD 8.4) and 20.3(SD 5.6) mg/kg/day and MTD was 20mg/kg/day. Despite MTD being the main treatment objective it was only achieved in 65 percent of the whole cohort. It was evident from our rate of transient myelosuppressive episodes that dosing was pushed to MTD, where possible, but patients were not able to tolerate high doses. None were able to maintain a dose anywhere near 30mg/kg/day, as the stated aim in the treatment protocol. Non compliance with HU and/or the treatment regime was the main source of MTD non achievement. HU was not routinely stopped by the medical team if patients were non compliant with the drug or the treatment monitoring schedule.

Non adherence to MTD and modest tolerance explains why the mean annual dose remained ≤ 20mg/kg/day. These doses are similar to the MSH, where two-thirds of adult patients in quartile 4, the most compliant and best responding group, averaged doses of between 15-22mg/kg/day (Steinberg et al, 1997). In contrast children appear to be able to achieve higher doses, with MTDs reaching at least 5-6 mg/kg/day more then in adults, possibly due to better bone marrow reserve, improved adherence to therapy and more rigorous monitoring (Kinney et al, 1999; Zimmerman et al, 2004; Hankins et al, 2005).

5.6.1 Optimal treatment regime

The results of different treatment strategies were compared, as shown in Table 5.2, to identify the optimal treatment regime for routine clinic practice. Unfortunately most studies have reported haematological responses with sparse clinical outcome data. If clinical outcomes (e.g. IP admissions, IP days, patient transfusion requirements or ACS events) were reported they were not easily comparable due to the different methods of analysis used by each study. Therefore, outcomes after two years of treatment were compared as these were consistently reported by most studies.

The evidence from the Belgium registry, the French cohort and the present study suggests that both haematological and clinical benefits are sustained up to two years with modest

daily doses of between 19 -20.7 mg/kg/day, as shown in Table 5.2. Similar to the present study these cohorts were followed up in normal clinical practice with less stringent monitoring than in the US cohorts, where patients received treatment as part of formal clinical trials. Notably patients, in the European cohorts, that were seen to be non compliant were not excluded and treatment and monitoring schedules were decided by the individual patient's clinician. The mean daily dose for the adults in quartile 3 and 4, of the MSH study, was 20mg/kg/day (Steinberg et al, 1997).

In contrast most of the US studies, involving children, have succeeded in maintaining HU at MTD or fixed doses of 30 -35mg/kg/day but with more stringent monitoring procedures including withdrawing treatment if patients are non compliant. The studies by Zimmerman et al (2004) and Kinney et al (1999) managed a mean daily dose of between 24.4 -25.6 mg/kg/day. In the HUSOFT extension study 21 children had their dose escalated to 30mg/kg/day after two years of HU at 20mg/kg/day (Wang et al, 2001; Hankins et al, 2005). All but one child managed to stay on this dose for up to four years.

Maintaining a HbF of 20% and Hb of 9g/dl are thought to be the thresholds that confer therapeutic benefit for SCD patients (Powers et al, 1984; Noguchi et al, 1988; Ohene-Frempong and Smith-Whitley 1997). The data in Table 5.2 shows that all cohorts, except the HUSOFT trial, were able to increase mean Hb to $\geq$ 9g/dl. The increase was not statistically significant in the French cohort. HbF% was also significantly increased, although only two of the cohorts achieved a HbF% $\geq$ 20%. Absolute neutrophil count was reduced in all the studies and, where reported, the reduction was statistically significant, except in the Belgian registry group. Only the European cohorts and the MSH reported differences in clinical outcomes achieved from pre-treatment. Number of IP days and number of pain crisis events were statistically significantly reduced after two years of treatment, where reported.

Table 5.2: Comparison of clinical and laboratory responses in sickle cell patient cohorts after 2 years of hydroxyurea therapy

	No. patients	Median age (yrs)	Dose objective	Dose (mg/kg/day)	HbF%	Hb (g/dl)	ANC (10⁹/l)	No. IP days	No. Pain crisis events
This study (NWL cohort)	31-46	28* 10*	MTD	19.3	18.3 p= 0.001	9.7 p= 0.002	4.5 p= 0.001	0** p= 0.001	1.03 p= 0.02
Gulbis et al (2005) (Belgian Registry)	88	6	Doctors' decision	21.7**	15.6*** p< 0.001	9 p< 0.001	4.5 NS	7.1 p< 0.001	
Wang et al (2001) (HUSOFT trial)	21	1.25	20mg/kg/day	20	20.3 NR	8.8 NR	4.2 NR		
Zimmerman et al (2004) (Duke cohort)	97	11.1	MTD	24.4	20.3 p< 0.001	9.6 p< 0.001	3.5 p< 0.001		
Kinney et al (1999) (HUG-KIDS trial)	35	9.1	MTD	25.6	15.5 NR	9 NR	4.6 NR		
De Montalembert et al (1997) (French cohort)	25	11	Set dose****	19	12.2 p= 0.0001	9.1 NS	5.3 p= 0.008	6 p= 0.0001	
Steinberg et al (1997) MSH, quartile 3	36	Adults	MTD	20*****	8.8 NR	9.1 NR	4.5 NR		3.1 NR
Steinberg et al (1997) MSH, quartile 4	35	Adults	MTD	20*****	18.1 NR	9.1 NR	3.6 NR		2.3 NR

Abbreviations: Hb = haemoglobin, ANC = absolute neutrophil count, IP = inpatient, NR = not reported, NS = not significant, ACS - acute chest syndrome

Mean annual values are reported unless otherwise stated

p - value corresponds to the statistical significance of the difference in the variable from baseline/pretreatment

* Median adult age and median child age at start of treatment

** Median reported

*** HbF= 1.4g/dl, converted using formula from Steinberg et al (2003): HbFg/dL =HbF%* Hbg/dL

**** HU was given on 4 consecutive days each week. The maximal dose was 40mg/kg/day

***** 50% of patients in Quartile 3 received ≥15 mg/kg/day and 88.6% of patients in Quartile 4 received ≥15mg/kg/day.

Two studies compared treatment regimes in the longer term. Gulbis et al (2005) compared a subset of their patients in receipt of HU for at least six years. They compared the clinical outcomes achieved from one to three years of therapy and from four to six years. Gulbis and colleagues (2005) found a tendency toward declining treatment intensity over time which was thought to result in HU being less effective in the long-term. The data presented in Tables 4.3 and 4.4 shows that the benefit achieved from pre-treatment with respect to mean annual IP pain crisis events and IP days were reduced over time in the NWL cohort. There was persistence to strive for MTD but dose reduction did occur over time, as shown in Table 4.3. Only 65% of patients were treated at MTD and the mean daily dose was very modest at between 18.1 to 20.3 mg/kg/day, the highest level achieved. Therefore there may have been some reduction in treatment intensity over time, in this NWL cohort. In addition, the mean daily dose achieved was below the optimal level, from the outset, for those patients not pushed to MTD.

Zimmerman et al (2004) compared the haematological outcomes achieved within their US patient cohort with the Belgium cohort reported by Ferster et al (2001). Patients were compared for up to five years on HU. The US cohort had statistically significant higher Hb, HbF% and MCV when compared to the Belgian cohort. The better haematological results were attributed to the difference in treatment regime. The primary difference between the two patient groups was goal of treatment. In the US study, patients were treated at MTD whereas the Belgium cohort was not pushed to MTD. This resulted in the Belgian study participants being treated at lower daily doses of HU compared to the US cohort (Zimmerman et al, 2004; Gulbis et al, 2005).

In light of this evidence it seems sensible to strive for MTD to ensure HU remains effective, but with a more realistic expectation of the doses patients can attain and maintain over time in normal clinical practice. Doses in adult patients appear to average around 20mg/kg/day and up to 25mg/kg/day in children. Adult patients may be able to achieve a slightly higher dose, similar to that achieved by children, if there was more stringent monitoring and improved management of non-compliance to treatment and treatment protocol.

5.6.2 Maintaining MTD as treatment goal

Maintaining MTD was challenging, which was similar to the experience of others, including the MSH where MTD was not determined in 43 percent of patients (Steinberg et al, 1997). A major barrier appears to be non compliance with treatment schedule, whereby patients do not attend clinic appointments or they fail to take their medication. No explicit explanation was given as to why so many failed to reach MTD in the MSH but many patients in quartiles 1 and 2 did not take their tablets (Steinberg et al, 1997). In other US studies, shown in Table 5.2, between 11 and 19 percent of children had their treatment stopped for non adherence. Adolescents and young adults are the most likely to prove non-compliant and stop HU (Zimmermann et al, 2004; Gulbis et al, 2005).

Patient non compliance not only affects the efficacy of HU but it appears to be a substantial contraindication for usage. In the survey by Zumberg and colleagues (2005) 80 percent of doctors stated that non-compliance was a very important or important barrier to prescribing HU. The study by Lanzkron et al (2006) reported that six of seven eligible patients not on HU had problems with compliance such as no regular out-patient follow-up and non adherence to prescribed treatment. This problem is insufficiently researched but it is thought that the frequency of appointments for monitoring is a major issue along with simply forgetting to take the medication (Hutchins-Pullins, 2008). According to Zimmerman et al (2004) patient compliance problems should be managed by coordinated efforts from the medical team and frequent contact with families to provide support and encouragement.

5.6.3 Interventions for monitoring treatment effectiveness in clinical practice

The effect of reduction in treatment intensity over time could be mistaken for loss of efficacy and lead to the patient or doctor stopping therapy. In view of this it is important to monitor patient response in relation to daily dose and level of compliance. This can be achieved for individual patients using an electronic patient record like the one produced by the present NWL SCD registry. The graphical presentation of results, as shown in Figure 4.5, presented longitudinal information, on a single sheet, covering patient daily dose, changes in blood indices, clinical outcomes and myelosuppressive toxic episodes. This concise and easy to read clinical management tool enables systematic monitoring in routine clinical practice.

Care providers and parents have reported uncertainty about HU effectiveness and efficacy as a barrier to use (Zumberg, et al 2005; Hankins et al, 2007). This clinical management tool has the potential to enable doctors, together with their patients, to systematically monitor treatment response over the duration of therapy. The UK Cystic Fibrosis Database provided software to participating sites to enable local data entry and analysis. A main output was individualized patient reports. These were successfully used during patient consultations to assist with clinical management and provide feedback to patients about their disease and care (Mehta et al, 2004). The cases reported in Chapter 4, section 4.2 provide anecdotal evidence of the benefit derived from the patient reports developed for the present NWL registry. This intervention would need to be formally tested before widespread implementation due to the inherent difficulties in implementing change to clinical practice. The evidence, in Chapter 2, suggests that even when a new treatment or instrument has proven efficacy, effective implementation strategies must be developed to motivate care providers to change clinical practice (Dellinger and Vincent, 2005; Department of Health, 2007a; Richards, 2007).

5.7 Managing patient attrition

Patient attrition rates were substantial in this study, similar to other HU patient cohorts (Kinney et al, 1999; Zimmerman et al, 2004; Gulbis et al, 2005; de Montalembert et al, 2006; Segal et al, 2008). This occurred because patients stopped treatment or were lost to follow-up.

5.7.1 Reasons for stopping HU

In this cohort medical contraindication was the reason for stopping therapy in nearly 50 percent of cases. Other studies have also reported that many patients ceased treatment for medical reasons (Kinney et al, 1999; Gulbis et al, 2005; de Montalembert et al, 2006). HU is reserved for the most severely affected SCD patients, often with multiple co-morbidities. Therefore it is inevitable that in some cases of disease progression HU will no longer be the optimal treatment choice. In addition there will always be instances were treatment is interrupted for social and lifestyle reasons such as pregnancy or fathering a child, rehabilitation for substance misuse and so forth.

Ten patients refused to continue with HU, out of the 23 which stopped, including three who decided not to restart following an interruption for pregnancy. It is not known why these patients decided to stop therapy. Unfortunately studies have not investigated why patients refuse HU, which is a major impediment in quantification of risks versus benefits. For example it is not known if patients stop because of inadequate response, development of adverse events, side effects or complications (Segal et al, 2008). In addition patients may have stopped for the same reasons cited as barriers to usage such as concerns about side effects, safety and efficacy of HU, or inability to comply with the treatment regime (Zumberg et al, 2005; Hankins et al, 2007).

5.7.2 Reasons for losses to follow-up

Thirty percent of patients were lost to follow-up by the registry during the data collection period. These patients were receiving treatment when follow-up ceased. Substantial losses to follow-up have also been reported by other HU studies in SCD patients (Strouse et al, 2008).

Losses to follow-up and other types of patient attrition have two effects on the data. Firstly they reduce the sample size and secondly non-random losses may introduce selection bias which can affect the validity and generalisability of the study results. Random losses do not affect the validity of the results but the reduction in sample size will weaken power and precision of the study (Mortensen, 1995; Grimes and Schulz, 2002b). Some losses to follow-up, in this study, were likely to be random but others may not have been. Data collection ceased in some hospitals due to lack of funding. The curtailment of data collection in these patients was non random but there is no reason to expect that these patients differed in any way from the cohort that continued to be followed up. Therefore their loss did not introduce selection bias into the cohort to invalidate the study results. However, without this cohort the sample size was reduced over time and consequently the results are less robust for later years. The wider confidence intervals for some of the mean differences achieved in later years suggests that results might be partly due to random error and small numbers.

The group of patients for which it is unknown why they were lost to follow-up may be different to the group that remained in the cohort. These patients could be similar to the

group of patients for which the reasons for refusal of treatment are unknown. Possible reasons include non attendance due to relocation, not wanting to continue to be followed up in clinic or not wanting to continue with HU. The loss of these patients could introduce selection bias into the study if they are indeed different to the cohort that continued with treatment and continued to be followed up.

5.7.3 Managing losses to follow-up and other sources of patient attrition

Grimes and Schulz (2002b) suggest that the best way of dealing with loss to follow-up is to avoid it. Clinical networks and long-term investment in sickle cell research would enable clinical registries to follow-up these patients as they move around (Ohene-Frempong and Smith-Whitley, 1997). For example the number of patients lost to follow-up in the present cohort would have been cut by over 40 percent and the total size of the cohort increased if the part-time registry co-ordinator post had continued to be funded. Maintaining record-linkage between data sources is an efficient method of increasing registry coverage and at the same time reducing the burden of data collection, as discussed in Chapter 2, which is a barrier to participation for clinicians (Mortensen, 1995).

Reducing attrition rates due to treatment refusal and losses to follow-up from non attendance at clinic are different issues and probably more difficult problems to overcome. These problems may be partly due to ineffective dissemination of information concerning risks and benefits of HU by health professionals to patients and patient advocacy groups. Hankins and colleagues (2007) have shown that children with severe SCD and their parents can identify their treatment preferences if given appropriate written and oral information from health professionals. The majority of participants, in their study, preferred HU treatment over either chronic transfusions or bone marrow transplant.

Researchers have previously identified a need to develop patient friendly and age-appropriate education tools about the benefits of treatment to overcome some of the barriers to usage (Zumberg et al, 2005). In addition a centralized resource centre for HU, for example a Web page, has been proposed as a forum to equip patients and parents with the information they need and to provide an opportunity for them to share their experiences (Hutchins-Pullins, 2008). Considering the continued underutilization of HU, high treatment

refusal and non compliance rates such initiatives are urgently required, particularly for adolescents and young adults.

5.8 Strengths and weaknesses of the study design

This study used patients as their own controls which is an alternative to using a comparison/control group. Other longitudinal studies of SCD patients on HU therapy have used this approach therefore it facilitated comparison with these studies. In addition it was easier to administer this study design in normal clinical practice. Patients on HU were monitored regularly and the registry used the patients' routine data for the evaluation. Blood tests results were elicited from the hospitals' information systems and clinical data was also routinely available from the hospital information systems and the patients' medical records.

Assimilating the findings of this study with other small studies of HU treatment in SCD patients will help clinicians assess the effectiveness and tolerability of HU in the absence of better evidence (de Montalembert et al, 2006; Brawley et al, 2008). Similar results in different populations with different study designs increase the likelihood that the findings have external validity (Grimes and Schulz, 2002a).

5.8.1 Controlling for confounders and information bias

There are several methodological weaknesses with this study design. First it is very difficult to identify if an observed complication or side effect, such as leg ulcer, is due to the treatment or the patients' underlying illness. This could be controlled for by comparing the cohort with a comparison group of SCD patients not on HU (Lanzkron et al, 2008). If both cohorts are followed up in the same manner then any observed difference in incidence rates between the groups could be regarded as a true difference.

However patients on a potentially toxic treatment, like HU, are often followed up rigorously for side effects and adverse events and therefore there is the potential for information bias resulting from over investigation or estimation of risk in the treatment group. Side effects and adverse events will be specifically looked for in the treatment

group. Consequently risks of treatment are more likely to be better recorded in this group than for patients not on treatment or, if using the patient as their own control, than in the pre treatment period. It is not feasible or ethical to blind the data collectors or patients to the exposure in normal clinical practice.

HU is underutilized for SCD patients and one of the main reasons is uncertainty about serious adverse events such as cancer risk, risk in pregnancy and risks to fertility (Brawley et al, 2008). Knowing the prevalence of HU use among SCD patients would help assess the relative risks of treatment (Brawley et al, 2008). This is only possible if there is reliable data on total numbers of SCD patients as well as the proportion being treated with HU. This can be achieved in the context of a registry, such as the NWL SCD registry, where all SCD patients are followed up, not just the group in receipt of HU therapy.

5.8.2 Managing effect of regression to the mean due to selection bias

The severity of SCD is very variable both between different patients and over the lifetime of individual patients. Patients are commenced on HU when they are severely ill therefore they could be experiencing a particularly severe period of the disease at the initiation of treatment which might revert back to steady state without any treatment. In this situation using the patient as their own control would over estimate the benefits of the treatment (Bland and Altman, 1994b).

Regression to the mean is the phrase used to identify the phenomenon that a variable that is extreme on its first measurement will tend to be closer to the center of the distribution for a later measurement (Davis, 1976; Bland and Altman, 1994b). If admission to a cohort includes a group with extreme measurements, such as high/low laboratory values or high number of adverse clinical events, then lower mean values will arise at follow-up whether treatment is administered or not (Bland and Altman, 1994b; Grimes and Schulz, 2002a). The more extreme the variable from the population mean the more room there is to regress to the population mean. The initial high abnormal results could have occurred through chance therefore there is high probably that subsequent measurements will spontaneously regress towards the population mean value (Bland and Altman, 1994b; Morton and Torgerson, 2003). This variability can be attributed to the inherent variation in the variable being measured (biological variation) and measurement error. It is a statistical phenomenon and always occurs in practice (Bland and Altman, 1994a).

This unavoidable selection bias must be considered when evaluating results from cohort studies, especially studies without a control group. Any true improvement due to treatment must be separated from the effect of regression to the mean (Davis, 1976; Criqui et al, 1983; Bland and Altman, 1994b). According to Grimes and Schulz (2002a) findings of strong associations suggest causation whereas weak associations, in observational studies, can easily be due to bias. Therefore the highly statistically significant results reported here can be considered a treatment effect ($p = 0.001$) whereas the smaller differences may or may not be real.

5.9 Registry growth and survival

A major structural problem with this registry was the lack of stable long-term funding. Due to lack of funding the registry was unable to expand coverage to other hospitals in the area and even maintain some of those hospitals already participating. Consequently the registry reverted back to a local, hospital based, clinical registry from a central registry, which aimed to cover the NWL region. The utility diminished due to the reduction in numbers of cases available for study and the potential decreased representativeness of the cohort because it became restricted to a single site.

On the whole clinical registries/ databases tend to have precarious funding streams (Black et al, 2004; Raftery et al, 2005). However, the literature, reviewed in Chapter 2, suggests that survival and growth in the long-term is dependent on adequate, regular and reliable funding and support from reputable organisations such as the Department of Health, local Primary Care Trusts, clinician representative bodies and voluntary patient advocate groups (Keogh, 2004; Mehta et al, 2004). A prerequisite for success includes a centralized team of core staff to co-ordinate the registry and manage the computing requirements together with adequate research support to recruit patients and to complete data collection at participating sites (Morris et al, 1997; Every et al, 1999; Mehta et al, 2004).

5.10 Conclusions

The experience reported here is a realistic example of what happens in normal clinical care settings. This study found that haematological benefits were maintained in the long-term with HU treatment but evidence of long term clinical effectiveness was less strong. This appeared to be due to the patterns of clinical management in everyday practice. Patients tend to be treated with modest doses due to intolerance or inability to attain or maintain MTD. Treatment protocols should be revised to reflect realistic dosing targets. There are significant barriers to optimal usage in routine clinical practice. Interventions need to be targeted at increasing utilisation, patient compliance and persistence with treatment. Special effort and creative thinking is required to devise methods to ensure the current literature on HU therapy filters through to patients, sickle cell advocacy groups and the healthcare community in general.

The North West London HU Sub- Registry has proved a useful tool to measure long-term safety and effectiveness of HU. The novelty of this study lay in examination of the nuances of HU treatment in everyday practice. This detailed information helped explain why clinical outcomes varied over time and identify factors that impact on treatment effectiveness. Comparison with other studies illustrates that these issues are not unique to this study. The results should help clinicians devise effective treatment protocols and strategies for managing patients commenced on HU.

A further innovation was the ability to use the routinely collected data for both clinical management purposes and research into SCD. The data enabled the development of a patient electronic record as a tool for clinical management. The information which enabled this study was relatively detailed but simple to collect. Most variables were routinely available from patient notes and hospital information systems. However, the study was conducted using stringent research methodology and required sufficient funding and research staff to administer.

National recognition of the need for comprehensive strategies for managing haemoglobinopathies in The National Plan (2000) provided the clout and impetus for current developments in services for SCD patients. The Antenatal and Neonatal Screening Programme for SCD and Thalassaemia was set up in 2001 and subsequently national

guidelines for the clinical care and management of adults and children with SCD were developed. A National Haemoglobinopathy Registry was recently established which provides the first opportunity for collecting population based data on incidence and prevalence of SCD in England. Taken together these initiatives should translate into better care and management of SCD patients with improved patient outcomes.

Establishing and maintaining successful registries/ clinical databases are fraught with difficulties. As stated in Chapter 2, registries are currently expected to collect better quality and more comprehensive and timely information in order that they are capable of more 'than basic analysis' (Keogh et al, 2004; Department of Health, 2007a). Comprehensive data collection for SCD can be achieved if registries operate as clinical information systems. Models, like the NWL Registry, with active involvement of local care providers in data collection and where there is the ability to keep and utilize their own data provides an incentive to maintain participation (Every et al, 1999; Mehta et al, 2004). Clinicians require regular data reports which will enable them to benchmark their local outcomes with the aggregate data from the whole registry, providing the opportunity for continuous quality improvement activities (English et al 1984; Every et al, 1999). This is considered an incentive to conduct careful patient selection and chart review. A participatory model with health professionals taking ownership and responsibility for improving patient care appears to be a successful strategy, provided there are objective outcomes to measure and monitor quality of care (Keogh et al, 2004; Society for Cardiothoracic Surgery in Great Britain & Ireland, 2008).

5.11 Recommendations for future research and development

i. Findings suggest that there is a need for further epidemiology/observational studies to be conducted into the diffusion and utilisation of HU treatment for SCD patients in routine clinical settings. In addition robust evidence is required on the long-term side effects of HU for this client group.

ii. This research should be conducted in the context of a clinical registry or registries, which follows all patients with SCD. A large registry cohort would enable case control studies to be undertaken and follow-up of patients in the long-term. The case control study design would allow true incidence of side effects to be calculated.

iii. SCD clinical registries should be set up as clinical information systems with local management and control by the patients' health care professionals. Data from these systems can be utilized locally for clinical care, research and audit. This data can then be uploaded to the National Registry for population based analysis. The model implemented by the Cardiac Surgical databases is a good example of how the system works in practice.

iv. Hospital based clinical information systems for SCD would provide the infrastructure for record linkage to other clinical systems enabling complete data capture during the patient's journey through the health care system.

v. Strategies should be developed to improve utilisation and compliance with HU treatment. The electronic patient record developed as part of this study requires multi-site evaluation for feasibility and benefit with patient monitoring during treatment. Other strategies, such as educational and information tools, should be developed in conjunction with patients and patient advocacy groups to improve understanding of HU benefits and risks. It may be that a qualitative in-depth study would be useful in ascertaining insight into patient refusal to continue or start HU therapy.

vi. National guidance on feasible HU treatment protocols and follow-up regimes would assist health care professionals to manage patients effectively throughout treatment. These should be comprehensive and flexible to capture the heterogeneity of SCD patients treated with HU.

Appendix I: SCD Protocols

Hydroxyurea (HU) in Sickle Cell Disease (SCD) Protocol

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Hydroxyurea (HU) in Sickle Cell Disease (SCD) Protocol

Introduction

Hydroxyurea has recently been licensed in the United States of America for use in severely affected patients with sickle cell disease. It is the first orally active agent that is well tolerated, and has been shown to ameliorate the clinical severity of sickle cell disease by decreasing the frequency of painful crises, reducing the number of episodes of acute chest syndrome, and reducing blood transfusion requirements. It increases the levels of fetal haemoglobin (HbF), improves red cell hydration, and reduces the degree of leucocytosis and thrombocytosis commonly seen in SCD. However, it is chemotherapeutic agent, thus patients receiving this agent require regular monitoring as it may cause myelosuppression in the short-term, and its long-term safety profile in haemoglobinopathy patients is unknown.

1. Patients   Adults and children with Sickle cell disease, who have:

i.	> 3 admissions with painful crises in the previous 12 months, or
ii.	> 1 admission with painful crisis in the previous 12 months, and are symptomatic in the community, or
iii.	> 2 life-threatening complications of the disease, such as acute chest syndrome, or
iv.	other indications as discussed with doctor

2. Exclusions i.   Pregnancy, or not practising active contraception
ii.   Active hepatitis

NB: **Caution is advised in treating children under the age of 2 years with this agent**

3. Obtain written consent

Explain present knowledge respecting side effects and toxicity, such as, cytopenias short-term and the unknown/unquantified long-term risk of leukaemia/malignancy.
Provide patient information sheet and obtain written consent from patient (and parent if under 18 years)

4. Dosage and myelosuppression

Hydroxyurea is available as 500mg capsules and as a suspension 100mg/ml:

In adults commence at 15 mg/kg to nearest 500 mg, in children commence at 15mg/kg increasing 4-weekly until:
the neutrophils < 2.0×10^9/L, or
the platelets < 80×10^9/L, or
the reticulocytes < 1%, or
the haemoglobin >3g/dl from baseline
Then stop the HU until the full blood count (FBC) has recovered - generally 1-2 weeks - checking the FBC weekly.
Restart at 2.5 mg/kg or 1 capsule (500 mg) daily lower. This is the maximum tolerated dose (MTD).

Pharmacy requires a chemotherapy prescription sheet to be completed with the first prescription

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5. Monitoring

i. Clinical   a.   Collection of routine data (clinical history, physical examination)
              b.   Last menstrual dates recorded
              c.   Side effects
There is a separate sheet for this purpose

ii. Laboratory investigations

At outset: FBC   U&Es
                        Quantitative electrophoresis   Liver function
                        Reticulocytes   LDH
                        Serum ferritin / clotting   Hepatitis B, C serology
                        ZPP

Every 14 days until MTD: FBC, Reticulocytes   Hb F
                        U&Es   Liver function

Every 14 days at MTD until stable (minimum 8 weeks).i.e. HbF, MCV have plateaued
              FBC, Reticulocytes   Hb F
                        U&Es   Liver function

Once stable 6-8 weeks
                        FBC   Hb F
                        U&Es   Reticulocytes
                        Liver function   LDH

6. Side effects

Expected   Bone marrow suppression → cytopenias
              Rise in haemoglobin and HbF
Warn patients to seek medical advice urgently for petechiae, bruising or bleeding

Common   Hyperpigmentation of nails

Rare   Nausea
              Vomiting
              Skin rash
              Alopecia
              Diarrhoea

7. Action to be taken if side effects occur

i.   Bone marrow suppression

If neutrophils < 2 x10^9/L ± platelets < 80 x 10^9/L ± reticulocytes < 1% ± haemoglobin >3g/dl below baseline

THEN   a.   Stop hydroxyurea
          b.   Recheck FBC twice weekly and restart HU at 500 mg lower dose than previously once
                neutrophils > 2 x 10^9/L and platelets and reticulocytes are in the normal range.
          c.   Consider GCSF or blood transfusion on discussion with medical staff

ii.   Rise in haemoglobin

Venesect if Hb rises to > 12g/dl or if rises to > 3 g/dl above baseline with symptoms of hyperviscosity

iii.   Other symptoms

Stop on patient's request

8. Follow up

Blood tests 6-8 weekly once stable
6 monthly medical review including annual review
Haemoglobinopathy Register
        patient information sheet and consent forms available
        registration and annual follow-up forms to be completed
GP guidelines on hydroxyurea to be sent

9. Literature

Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332**: 1317-1322

Safety of hydoxyurea in children with sickle cell anemia: Results of the HUG-KIDS Study, a phase I/II trial. *Blood* 1999; **94(5)**: 1550-1554

Appendix II: SCD Documents

Study Definitions & Associated Grading Tables for SCD Registry

HAEMOGLOBINOPATHY REGISTRY
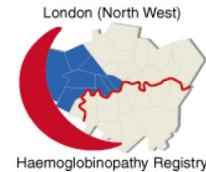
Study Definitions & Associated Grading Tables
for Sickle Cell Disease Registry

Definitions of clinical events and relevant grading tables have been compiled to assist with completing questionnaires. **Participants are required to adhere to these operational definitions to ensure consistency in data collection and enable comparison of findings with other studies.** *To aid comparability definitions correspond with those used in previous research, particularly the Cooperative study of Sickle Cell Disease (CSSCD) (Platt OS et al 1994, Gill et al 1995) and Miller et al (2000) and, where possible, standardised grading tables are included.*

Acute chest syndrome (ACS) - lung consolidation and X-ray changes caused by infection, infarction or fat embolus, generally associated with chest wall pain, dyspnoea and a fall in pAO2 (Golden C et al 1998, Vichinsky EP et al 2000, Platt OC 2000).

For the purposes of the haemoglobinopathy registry a diagnosis of ACS should be made each time a patient develops a new infiltrate on chest X-ray film or a defect on radionuclide imaging of the chest, in combination with fever or respiratory symptoms (Gill et al, 1995).

Aplastic crisis - a fall in haemoglobin ≥ 2 gr./dl and reticulocytopenia, not caused by sequestration of blood in organs. The most common cause is infection of developing erythroblasts with parvovirus B19, which can be confirmed either by electron microscopy of the serum or presence of specific IgM (Pattison et al, 1981).

Avascular necrosis (hip or shoulder) - necrosis of long bones due to bone marrow infarction. There are *early radiographic changes*, which may be diagnosed on X-ray, but MRI is the definitive investigation (Roberts-Harewood M & Davies SC 1998). Ficat & Arlet (1980) classified the radiological changes seen in the femoral head as follows:

Table 1: Avascular Necrosis of Femoral Head: Staging Criteria

Stage I	Slight osteoporosis
Stage II	Osteoporosis or osteosclerosis
Stage III	Early flattening and collapse
Stage IV	More gross damage

Chronic Sickle Lung - the development of pulmonary fibrosis leading to restrictive lung changes resulting from recurrent episodes of ACS or chronic pulmonary sickling (Roberts-Harewood M & Davies SC 1998). Finally pulmonary hypertension and *cor pulmonale* ensues. Powers et al (1988) define the progression of the disease as follows:

SCD Registry Study Definitions & Associated Grading Tables

Table 2: Sickle Chronic Lung Disease – Staging Criteria

	Stage 1	Stage 2	Stage 3	Stage 4
Chest pain	Recurrent substernal pain and chronic cough	Increased pain over Stage 1	Severe midline crushing pain	Severe and prolonged pain with dyspnoea at rest
Blood gases	Normal oxygen saturation	Normal oxygen saturation	Hypoxia with partial pressure oxygen (70 mg Hg) during stable periods	Partial pressure oxygen (60 mg Hg) during stable periods
X-ray	Decreased distal pulmonary vascularity, hyperexpansion, evidence suggestive of increased interstitial markings	Diffuse, fine interstitial fibrosis involving all lobes of the lung	Pulmonary fibrosis	Severe pulmonary fibrosis
Pulmonary function tests*	Decreased FVC, TLC, FEV$_1$, and FEV$_1$/FVC ratio (mild, 80% of predicted normal, or 1 SD below normal)	Decreased FVC, TLC, DCD, FEV$_1$, and FEV$_1$/FVC ratio (moderate, 60% of predicted normal, or 2 SD below normal)	Decreased FVC, TLC, DCO, FEV$_1$, and FEV$_1$/FVC ratio (severe, 40% of predicted normal, or 3 SD below normal)	Patient frequently unable to complete testing due to degree of hypoxia
ECG and ECHO	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement. Progressive increase in heart size	Severe right ventricular and right atrial hypertrophy. ischaemic T waves in V1 and V2 and cor pulmonale.
Pulmonary artery pressure	Normal	Normal	Borderline elevation or normal	Markedly elevated with pulmonary hypertension

* These measurements are based upon common methods for comparison of reference values.
Abbreviations: FVC = forced vital capacity, TLC = total lung capacity, FEV$_1$ = forced expiratory flow rate

Dactylitis (hand/foot syndrome) - sickle vaso-occlusion of the metacarpals or metatarsals with overlying soft tissue involvement (Davies SC & Wonke B, 1991). *For the haemoglobinopathy registry an episode of dactylitis is defined as pain and tenderness, with or without swelling, in the hands and/or feet, generally in children* (Gill *et al* 1995, Miller *et al* 2000).

Ethnic origin - this study is using the new ethnic codes, used in the National Census 2001. [See Appendix 1 for a fuller explanation of ethnic categories.]

Epileptic fits - major or minor motor(generalized or temporal lobe) seizures, not stroke or meningitis (Platt OS *et al* 1994).

Febrile episode - documented temperature of $> 38.3\ ^0$C oral (Platt OS *et al* 1994).

Gallstones - Gallstones are common in sickle cell disease due to chronic haemolysis (Serjeant G, 1992). For further information on symptomatic biliary tract disease see Webb et al (1989) and Bond et al (1987).

Hearing Impairment - patients with SCD have an increased risk of hearing loss due to sickling, infection (causing conductive hearing loss) and ototoxic medications such as desferrioxamine. It is postulated that sensorineural hearing loss in SCD patients results from the tissue hypoxia caused by sickling in the cochlear venous system.. Hearing impairment is usually transient but may be long-term. *For this study the diagnosis of hearing impairment should be made by a formal Audiology assessment.* In contrast, sudden hearing loss in a patient with SCD represents a sickling crisis of the intracranial circulation (labyrinthine capillary bed) (Schreibstein *et al*, 1997).

Headache - those complaining of severe, usually throbbing headache that interferes with daily functioning and which occurs at least once in each month (Pavlakis SG *et al* 1989).

Hepatic sequestration - a documented acute enlargement of the organ with a fall in Hb of ≥ 2 gm/dl and no reticulocytopenia, which may be associated with infection (Davies SC & Brozović M 1989, Hatton CSR *et al* 1985). There is usually associated bone pain and clinical progression is generally less acute then in splenic sequestration, developing over a few hours to days (Davies SC & Brozović M 1989).

Leg ulcers - skin ulcer on lower legs or ankles, unhealed in 14 days (Platt OS *et al* 1994).

Meningitis - abnormal cerebrospinal fluid (CSF) findings and culture or serological positive CSF (Gill *et al*, 1995).

Mesenteric Syndrome - abdominal pain and distension with ileus and absent bowel sounds caused by vaso-occlusion in the blood supply to the gut and is self limiting (note not bowel infarction) (Davies SC & Wonke B, 1991).

Painful vaso-occlusive crisis results from microvasculature obstruction causing hypoxia and pain generally in the bones but also in joints, muscles and on occasions soft tissues (Davies SC & Wonke B, 1991). The pain may vary from mild to excruciatingly severe.

A painful event is defined here as pain in the arms and legs, back, abdomen, chest or head that lasts at least two hours, leads to a request for medical intervention, and for which no other explanation is found (e.g. osteomyelitis or appendicitis) (Miller *et al* 2000, Gill *et al* 1995).

Pica - a perverted craving for non-nutritious or even harmful substances unfit for food e.g. chalk, paper, coal e.g., symptomatic or some diseases and often noted in pregnancy (Spiegl F 1996).

Priapism - a prolonged painful erection of the penis that is not associated with sexual desire but caused by sickling in the corpora cavernosa and is almost certainly due to occlusion of the outflow vessels (Monga M *et al*, 1996, Davies SC & Brozović M 1989). Priapism may be an indicator of severe sickle disease expression (Sharpsteen JR *et al*, 1993).

Table 3: Priapism -description of episodes

Stuttering	> 2 events lasting < 6 hours, and settling spontaneously.
Fulminant	Event lasting > 6 hours.
N/A	Not applicable (female patient).

Prognathia - a characteristic deformity of the face due to expansion of the bone marrow within the facial bones. The erythroid hyperplasia of the bone marrow causes marked dilatation of the marrow spaces within the maxilla, which may result in distortion of the facial bones (Huntsman 1987).

Proliferative sickle retinopathy -changes in the retina due to vascular damage caused by SCD, which are grouped into *nonproliferative* and *proliferative*. Infarction of the peripheral retina results in the proliferation of fragile thin-walled blood vessels 'sea fans' at high risk of bleeding (Castro O, 1999). The development of this neovascularization is the distinguishing feature of proliferative sickle retinopathy; the progression of which has been defined by Goldberg (1971) (see table 4).

Table 4: Proliferative Sickle Retinopathy: Staging criteria

Stage 1:	Peripheral arteriolar occlusions
Stage 2:	Peripheral arteriolar-venular anastomoses
Stage 3:	Neovascular and fibrous proliferations
Stage 4:	Vitreous haemorrhage
Stage 5:	Retinal detachment

Puberty - a series of physical and physiological changes through which children pass to achieve adult development. The physical events include a growth spurt, alteration of body proportion and the development of sexual organs and secondary sexual characteristics. Previous studies suggest that a haemoglobinopathy results in delayed growth and sexual development (Platt OS et al, 1984). A standardised scheme for recording genital, breast and pubic hair maturation has been described by Tanner (Table 5) (Hull & Johnston 1987).

SCD Registry Study Definitions & Associated Grading Tables

Table 5: Sexual Development - Tanner Stages

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
	Boys:				
Genital development	Testes, scrotum, and penis are about the same size and proportion as in early childhood	Enlargement of scrotum and testes. Skin of scrotum reddens and changes in texture. Little or no enlargement of penis	Enlargement of penis; mainly in length. Further growth in testes and scrotum	Increased size of penis with growth in breadth and development of glands. Testes and scrotum larger; scrotal skin darkened	Genitalia adult in size and shape
	Girls:				
Breast development	Elevation of papilla only	Breast bud stage: elevation of breast and papilla as small mound. Enlargement of areola diameter	Further enlargement and elevation of breast and areola with no separation of their contours	Projection of areola and papilla to form a secondary mound above the level of the breast	Mature stage: projection of papilla only due to recession of the areola to the general contour of the breast
	Both sexes:				
Pubic hair	No pubic hair	Sparse growth of long, slightly pigmented downy hair, straight or slightly curled, chiefly at the base of the penis or along the labia	Considerably darker, coarser and more curled. Hair spread sparsely over the junction of the pubes	Adult in type but area covered smaller than in adult	Adult in quantity and type
Axillary hair	No axillary hair	Scanty growth of slightly pigmented hair	Hair adult in type and quantity		

Renal failure - 20% increase in baseline creatinine level and creatinine clearance < 100 ml per minute (Platt OS *et al* 1994). Routine renal function will be monitored through results of routine blood and urine testing.

Sepsis - positive blood culture (Platt OS *et al* 1994).

Sickle teeth (Paediatric Questionnaire only) - discoloured horizontal bands across teeth, not due to caries. This probably results from vaso-occlusion occurring at the time of dental enamel being laid down.

Skeletal/joint event (e.g. Osteomyelitis) - acute pain involving one or more bones that lasts at least 7 days or non traumatic swelling of one or more joints with pain or effusion (Gill *et al*, 1995). Osteomyelitis is identified with an etiological agent by culture.

Splenic sequestration (Acute) (ASS)- a documented acute enlargement of the spleen with a fall in Hb of ≥ 2 gm/dl and evidence of marrow activity (i.e. increase in reticulocytes), due to pooling of blood within the organ (Topley JM *et al* 1981, Roberts-Harewood M & Davies SC 1998). Topley et al (1981) differentiate between **classic life-threatening episodes characterized by peripheral circulatory failure** and minor **episodes without evidence of peripheral circulatory shock but characterized by increasing anaemia in association with an enlarging spleen and an active marrow.** These minor episodes, which present as less dramatic haematological and clinical changes, form a continuous spectrum with the 'classical attacks.

<div align="center"><u>OR</u></div>

Miller *et al* (2000) define ASS as a decrease from the baseline in the haemoglobin level or hematocrit of at least 20 percent plus a simultaneous increase in the spleen size to at least 2 cm below the left costal margin.

Splenic sequestration (Chronic hypersplenism), where splenic enlargement is sustained (for more than 3 months) with chronic red cell sequestration, compensatory marrow expansion, and a new haematogical equilibrium (Hb drops by ≥ 1gm and reticulocytes generally exceed 20%) (Serjeant & Serjeant, 1993).

Stroke - an acute neurologic syndrome due to vascular occlusion or haemorrhage in which neurologic symptoms or signs last more than 24 hours (Miller *et al*, 2000). Transient ischaemic attacks and silent infarctions are not included.

Transient ischaemic attacks (TIAs) - same as stroke except lasting < 24 hours.

Urinary tract infection -urine culture of > 20 white cells per high-power field or > 10^5 colonies per millilitre of bacteria (Platt OS *et al* 1994).

SCD Registry Study Definitions & Associated Grading Tables

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SCD Registry Study Definitions & Associated Grading Tables

APPENDIX 1

Ethnic Codes (Source: Office of National Statistics, December 2000)

Ethnic Group Classifications

The new UK classifications are: White
Mixed
Asian or Asian British (or Asian Scottish in Scotland)
Black or Black British (or Black Scottish in Scotland)
Chinese or other Ethnic Group

Ethnic Group sub divisions for the UK

These five major classifications encompass the 16 UK sub classifications described in the haemoglobinopathy registry questionnaires. The following **Detailed Codes** will assist with completing the ethnic group accurately.

White	Asian or Asian British
British	Indian or British Indian
Irish	Pakistani or British Pakistani
English	Bangladeshi or British Bangladeshi
Scottish	Mixed Asian
Welsh	Punjabi
Cornish	Kashmiri
Cypriot (part not stated)	East African Asian
Greek	Sri Lankan
Greek Cypriot	Tamil
Turkish	Sinhalese
Turkish Cypriot	British Asian
Italian	Other Asian, Asian unspecified
Irish Traveller	
Traveller	
Gypsy/Romany	
Polish	
All republics which made up the former USSR	
Kosovan	
Albanian	
Bosnian	
Croatian	
Serbian	
Other republics which made up the former Yugoslavia	
Other white Europeans	
South American	
Mixed White	
Other white, white unspecified	
Mixed	**Black or Black British**
White and Black Caribbean	Caribbean
White and Black African	African
White and Asian	Somalian
Black and Asian	Mixed Black
Black and Chinese	Nigerian
Black and White	Black British
Chinese and White	Other Black, Black unspecified
Asian and Chinese	
Other Mixed, Mixed unspecified	
Chinese or Other	
Chinese	
Africa - colour not defined	
Middle East	
Vietnamese	
Japanese	
Filipino	
Any Other Group	

Further information may be obtained from the Office of National Statistics:
Tel: +44 (0) 1329 813703   Website: www.statistics.gov.uk

Appendix III: SCD HU Proformas

Proforma 1: HU Registration

European Haemoglobinopathy Register
Hydroxyurea and/or Deferiprone Patient Data
Registration Only

52248

Write in black ink, using clear CAPITALS.

NHS No	* Hospital No.
* Last Name	
* First Name	
* Date of Birth	/ /
* Date Started	/ / * MUST be completed for ALL patients
* Sex	○ M ○ F
* Weight	. kg

Drug Regime   *Hydroxyurea (HU) & Deferiprone (L1)*

HU Daily Dose	mg/day
HU Dose Objective	○ Max. tolerated dose ○ Set dose If Set Dose, state Objective . mg/kg/day
Was HU Refused in the Past	○ No ○ Yes Year HU Refused

Reason HU Started
☐ Stroke ☐ Other CNS Event ☐ Recurrent IP Pain Crisis ☐ Symptomatic in Community
☐ Chronic Sickle Lung ☐ Fulminant Priapism ☐ Recurrent Priapism ☐ Chronic Renal Failure
☐ Iron Overload ☐ Leg Ulcers ☐ Severe Anaemia/Haemolysis ☐ ACS
☐ AVN ☐ Patient/Parent Request ☐ Liver Disease ☐ Splenic Sequestration
☐ Poor Venous Access ☐ Alternative to Tx Prog ☐ Other

Other Reason HU Started	
L1 Daily Dose	mg/day
Reason L1 Started	☐ Iron Overload ☐ Desferal Contra-Indicated ☐ Desferal Toxicity ☐ Prescribed with Desferal ☐ Other
Other Reason L1 Started	
Other Hb F Stimulating Drugs	
Growth Factor	☐ EPO ☐ GCSF ☐ GMCSF ☐ Other
Vitamin C	○ No ○ Yes

Laboratory Result - At Baseline

WBC	. 10^9/l	Retics	. %	Protein (Total)	g/L
RBC	. 10^12/l	Retics (Abs)	10^9/l	Albumin	g/L
Hb	. g/dl			gGT	IU/L
MCV	. fl	Sodium	mmol/L	LDH	IU/L
MCH	. pg	Potassium	. mmol/L	Ferritin	ug/L
MCHC	. g/dl	Creatinine	umol/L	CRP	mg/l
RDW (CV)	. %	Urea	. mmol/L	Corr. Ca	. mmol/L
RDW (SD)	. fl	AST	IU/L	Zinc	umol/l
Platelets	10^9/l	ALT	IU/L	Vit B12	pg/ml
Neutrophils	. 10^9/l	Alk. Phos	IU/L	RC Folate	ng/ml
NRBC	/100	Bilirubin (Total)	umol/L	ESR	mm/hr
Other Blood Test					
Hb F	. %	Hb S	. %	Hb A2	. %
Hb (Other)	. %	Hb C	. %	Hb A	. %
Hb (Other Variant)					

Completed By   Date   / /

European Haemoglobinopathy Register
Hydroxyurea and/or Deferiprone Patient Data

52248

Registration Only

Write in black ink, using clear CAPITALS.

NHS No [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]   * *Hospital No.* [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

* *Last Name* [ ]

* *First Name* [ ]

* *Date of Birth* [ ][ ] / [ ][ ] / [ ][ ][ ][ ]   * *MUST* be completed for ALL patients

Pre Treatment History - In Previous 12 Months

Hair Thinning	O Absent	O Mild	O Moderate	O Severe
Skin Changes	O Absent	O Mild	O Moderate	O Severe
Nausea / Vomiting	O Absent	O Mild	O Moderate	O Severe
Nail Pigmentation	O Absent	O Mild	O Moderate	O Severe
Headaches	O No	O Yes	*Defined as severe headaches occuring at least once per month*	

Neutropenia (Neuts < 2 x 10^9l) O No   O Yes   No. of Episodes O 0 O 1 O 2 O 3 O 4

Thrombocytopenia (Plats < 80 x 10^9/l) O No   O Yes   No. of Episodes O 0 O 1 O 2 O 3 O 4

Reticulocytopenia (Retics < 1%) O No   O Yes   No. of Episodes O 0 O 1 O 2 O 3 O 4

Past Malignancy History O No   O Yes   Date [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Malignancy Type [ ]

IP Admissions In Previous 12 Months

IP O No   O Yes   No. of IP Admissions [ ][ ][ ]   No. of IP Days [ ][ ][ ]   *Day=overnight stay or > 24 hours*

Hospital □ CMH □ Eal □ Ham □ Hill □ NPH □ WMUH □ SMH □ C&W □ CharX □ MRI □ OLHSC □ Other

Other Hospital [ ]

Blood Tx in Last 12 months O None   O Sporadic   O Regular

Current Issues & Examination

Pregnant (Patient or Partner) O No   O Yes   Expected Delivery Date (EDD) [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Enter No. of outcomes in relevant box(es):

Previous Pregnancy(ies) [ ] Live Birth(s) [ ] Still Birth(s) [ ] Miscarriage(s) [ ] Termination(s) [ ]

Type of Fetal Anomaly (If Applicable) [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Comments/Problems [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Date of LMP [ ][ ] / [ ][ ] / [ ][ ][ ][ ]   Contraception O No   O Yes   O N/A

* *Next Appointment* [ ][ ] week(s)

Completed By [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] Date [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Page 2 of 2

Proforma 2: HU Follow-up

European Haemoglobinopathy Register *Follow-Up*

Hydroxyurea and/or Deferiprone Patient Data

55136

Write in black ink, using clear CAPITALS.   * *MUST be completed for ALL patients*

NHS No		* *Hospital No.*
* *Last Name*		
* *First Name*		
* *Date Seen*	/ /	* *Weight* . kg

Drug Regime & Adherence   *Hydroxyurea (HU) & Deferiprone (L1)*

Note: If drugs stopped, please enter 0 for Dose. If stopping for more than 3 months, please also complete Annual Follow-Up.

Current HU Daily Dose	mg/day	HU Doses Missed average per week
Current L1 Daily Dose	mg/day	L1 Doses Missed average per week
Other Hb F Stimulating Drugs		
Growth Factor	☐ EPO ☐ GCSF ☐ GMCSF ☐ Other	
Vitamin C	○ No ○ Yes	

Laboratory Results

WBC	. 10^9/l	Retics . %	Protein (Total)	g/L
RBC	. 10^12/l	Retics (Abs) 10^9/l	Albumin	g/L
Hb	. g/dl		gGT	IU/L
MCV	. fl	Sodium mmol/L	LDH	IU/L
MCH	. pg	Potassium . mmol/L	Ferritin	ug/L
MCHC	. g/dl	Creatinine umol/L	CRP	mg/l
RDW (CV)	. %	Urea mmol/L	Corr. Ca	. mmol/L
RDW (SD)	. fl	AST IU/L	Zinc	umol/l
Platelets	10^9/l	ALT IU/L	Vit B12	pg/ml
Neutrophils	. 10^9/l	Alk. Phos IU/L	RC Folate	ng/ml
NRBC	/100	Bilirubin (Total) umol/L	ESR	mm/hr
Other Blood Test				
Hb F	. %	Hb S . %	Hb A2	. %
Hb (Other)	. %	Hb C . %	Hb A	. %
Hb (Other Variant)				

Since last Outpatient Department Visit

IP Admission ○ No ○ Yes	No. of IP Days *Day = overnight stay or > 24 hours*
Hospital ☐ CMH ☐ Eal ☐ Ham ☐ Hill ☐ NPH ☐ WMUH ☐ BGH ☐ SMH ☐ C&W ☐ Char X ☐ Other	
Other Hospital	
IP Diagnosis ☐ Pain Crisis ☐ ACS ☐ Stroke ☐ Hep. Seq. ☐ ASS ☐ Mesent. Syn. ☐ Aplastic Cris. ☐ Other	
Description	
CPAP ○ No ○ Yes	Ventilated ○ No ○ Yes
Blood Tx ☐ None ☐ Top Up ☐ Exchange	Venesection ○ No ○ Yes Units Out
Pain in the Community ☐ No ☐ Pain Crisis ☐ Chronic ☐ Other	
Pain Description	
Comments/Problems	
Date of LMP / /	Contraception ○ No ○ Yes ○ N/A
* *Next Apppointment* week(s)	

Completed By	Date / /

Please complete Annual Follow-Up when required (This may be on the reverse of this proforma)

Proforma 3: HU Annual Follow-up

European Haemoglobinopathy Register
Hydroxyurea and/or Deferiprone Patient Data
Annual Follow-Up

24900

Write in black ink, using clear CAPITALS.

NHS No	* *Hospital No.*

* *Last Name*
* *First Name*
* *Date Seen* / /   * *MUST* be completed for ALL patients
OR *Date of Death* / /
Cause of Death

Drug Regime & Adherence — *Hydroxyurea (HU) & Deferiprone (L1)*

HU Dose Objective ○ Max. tolerated dose ○ Set dose   Set Dose Objective [ ].[ ] mg/kg/day

Note: Please enter date stopped if patient stopping HU permanently or for more than 3 months.

HU Date Stopped / /

Main Reason Stopped:
- ○ Stroke   ○ Other CNS Event   ○ Non Adherence
- ○ Non Responder   ○ Idiosyncratic Reaction   ○ Refused Rx
- ○ Started Tx Prog   ○ Starting Family/ Pregnant   ○ Death
- ○ Lost to FU   ○ Alternative Rx Started   ○ Other

Other Reason HU Stopped

Note: Please enter date stopped if patient stopping L1 permanently or for more than 3 months.

L1 Date Stopped / /

Main Reason Stopped:
- ○ Non Adherence   ○ Starting Family/ Pregnant   ○ Hypersensitivity to L1
- ○ Recurrent Neutropenia   ○ Agranulocytosis   ○ Breast Feeding
- ○ Ferritin<500ug/L   ○ Death   ○ Lost to FU
- ○ Alternative Rx Started   ○ Other

Other Reason L1 Stopped

History - Since Registration or Last Annual Follow - Up

Hair Thinning	○ Absent	○ Mild	○ Moderate	○ Severe
Skin Changes	○ Absent	○ Mild	○ Moderate	○ Severe
Nausea / Vomiting	○ Absent	○ Mild	○ Moderate	○ Severe
Nail Pigmentation	○ Absent	○ Mild	○ Moderate	○ Severe
Headaches	○ No	○ Yes	*Defined as severe headaches occuring at least once per month*	

Past Malignancy History ○ No ○ Yes   Date / /
Malignancy Type

Pregnant (Patient or Partner) ○ No ○ Yes   Expected Delivery Date (EDD) / /
Outcome(s) Live Birth(s)   Still Birth(s)   Miscarriage(s)   Termination(s)
Type of Fetal Anomaly (If Applicable)

Completed By   Date / /

Proforma 4: Inpatient Admissions

Inpatient Admissions Prior to Registration

37626

Complete Additional Proformas as Required

NHS No.		
Hospital No.		
Last Name		
First Name		

1 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or >24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

2 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or > 24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

3 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or >24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

4 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or >24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

5 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or >24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

6 Date `/` MM/YYYY
Hospital
Reason for Admission

No. of IP Days — *Day = overnight stay or >24 hours*
Blood Tx ☐ No ☐ Top up ☐ Exchange   **CPAP** ○ No ○ Yes   **Ventilated** ○ No ○ Yes

Date Completed

☐☐ / ☐☐ / ☐☐☐☐

Signature of Data Collector

Appendix IV: HU Patient Report

HU Patient Report

London (North West) Haemoglobinopathy Registry

NHS

NHS No:	1234567890		Hospital ID No:	1234567
Patient:	Firstname SURNAME		HU Status:	Unchanged - 28/04/2004

Hydroxyurea Report (03/10/2001 - 28/04/2004)

Haematology

Date		Months on HU	Weight	ΔWeight	Daily Dose	Dosage (mg/kg/day)	Dose Status	Date Stopped	Doses Missed per Week	WBC	RBC	Hb	ΔHb	MCV	MCH	MCHC	RDW %	RDW SD	Platelets	Neuts	NRBC	Retics %	Retics Abs
03/10/2001			81.0		1750	22				15.5	3.49	8.3		78.1	25.6	32.8	23.0		398	10.23		4.9	171.0
*12 Months	Summary	12	92.0	11.0	1000	11	Unchanged		0	8.4	3.06	10.2	1.9	103.1	33.3	32.3	21.5	n/a	200	4.65	n/a	3.3	100.9
*24 Months	Summary	24	95.0	14.0	1000	11	Unchanged		n/a	7.6	3.11	10.4	2.1	105.3	33.4	31.7	21.2	n/a	169	4.15	n/a	3.3	103.0
*36 Months	Summary	32	94.5	13.5	750	8	Unchanged		0	8.6	3.13	10.1	1.8	101.3	32.3	31.9	21.2	n/a	201	6.54	n/a	4.0	125.0

Biochemistry / Haemoglobin fractions

Date		Months on HU	Hb F	Hb S	Hb C	Hb A2	Hb A	Hb Other	Na	K	Urea	Creatinine	AST	ALT	gGT	Bilirubin Total	Protein Total	Albumin	Alk. Phos.	LDH	ZPP	Serum Fe	TIBC	Ferritin	Serum B12	Red Cell Folate	PT	PTTK
03/10/2001			22.5						141	4.2	4.5	109	66			77			101	891								
*12 Months	Summary	12	43.5	49.5	n/a	4.4	3.2	n/a	140	4.1	5.0	93	36	n/a	n/a	22	n/a	45	77	496	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
*24 Months	Summary	24	46.0	n/a	n/a	n/a	n/a	n/a	141	4.7	5.1	103	102	n/a	n/a	25	n/a	44	73	535	n/a	n/a	n/a	1170	n/a	n/a	n/a	n/a
*36 Months	Summary	32	40.1	n/a	n/a	n/a	n/a	n/a	141	4.3	4.5	97	70	n/a	n/a	25	n/a	44	69	524	n/a	n/a	n/a	n/a	n/a	911	15.6	n/a

Inpatient / Clinical

Date		Months on HU	IP	IP No Days	Blood Tx	Units In	Units Out	Vene-section	Date of LMP	Contraception	Follow-up Appoinment (Weeks)	IP Diagnosis	Pain in Community	Pain in Community Description	Calculated Toxic Episodes
03/10/2001			5	55 CMH	Sporadic	3	n/a				2	Other=Lap Chole, Gallbladder Disease, ERCPS	Yes	Throbbing pains all	
*12 Months	Summary	12	2	3		0	n/a					Other2			0
*24 Months	Summary	24	0	0		0	n/a								0
*36 Months	Summary	32	0	0		0	n/a								0

Comments/Problems: Repeat biliary problems, c/o Lethargy

NHS

London (North West) Haemoglobinopathy Registry

NHS No:	1234567890
Hospital ID No:	1234567
Patient:	Firstname SURNAME
HU Status:	Unchanged - 28/04/2004

Date	Birth Date	Months on HU	Weight	ΔWeight	Daily Dose	Dosage (mg/kg/day)	Dose Status	Date Stopped	Doses Missed per Week	WBC	RBC	Hb	ΔHb	MCV	MCH	MCHC	RDW %	RDW SD	Platelets	Neuts	NBC	Retics %	Retics Abs	Hb F	Hb S	Hb C	Hb A2	Hb A	Hb Other
03/10/2001			81.0		1750	22	Unchanged			16.5	3.49	8.3		78.1	25.6	32.8	23.0		398	10.23		4.9	171.0	22.5					
17/10/2001			83.0	2.0	1750	21	Unchanged			10.6	2.96	7.8	-0.5	85.4	26.5	31.0	25.8		264										
31/10/2001			83.0	2.0	1500	18	Decreased			7.9	2.50	7.8	-0.5	95.9	31.0	32.3	27.8		134	2.92				33.8					
07/11/2001			85.0	4.0	1000	12	Decreased			6.7	2.41	7.5	-0.8	97.4	31.3	32.1	27.2		145	3.42									
21/11/2001			85.0	4.0	1000	12	Unchanged			6.4	2.24	7.3	-1.0	100.6	32.6	32.4	25.3		219	3.53		2.0	44.8	41.0					
+2 Months		2	84.0	3.0	1313	16	Unchanged		n/a	7.9	2.53	7.6	-0.7	94.8	30.4	32.0	26.5 n/a		191	3.29	2	2.0	44.8	37.4 n/a	n/a	n/a	n/a	n/a	n/a
02/01/2002			86.0	5.0	1000	17	Increased			8.1	2.80	9.2	0.9	101.0	33.0	32.6	21.7		121	4.21				44.4					
+4 Months		4	86.0	5.0	1500	17	Increased		n/a	8.1	2.80	9.2	0.9	101.0	33.0	32.6	21.7 n/a		121	4.21 n/a		n/a		44.4 n/a	n/a	n/a	n/a	n/a	n/a
13/02/2002			91.0	10.0	0	0	Stopped	13/02/2002		6.2	1.91	7.2	-1.1	110.6	37.9	34.2	24.0		86	2.25									
27/02/2002			91.0	10.0	0	0	Stopped	27/02/2002		7.0	1.70	6.2	-2.1	110.4	36.7	33.2	22.8		129	3.04									
13/03/2002			91.0	10.0	0	0	Restarted			5.7	2.78	9.2	0.9	102.9	33.3	33.3	24.5		304	2.16				38.4					
27/03/2002			91.0	10.0	1000	11	Unchanged			7.6	3.10	10.3	2.0	98.8	33.2	33.6	23.4		375	3.65									
+6 Months		6	91.0	10.0	500	6	Unchanged		n/a	6.6	2.37	8.2	-0.1	105.7	35.3	33.3	23.7 n/a		224	2.78 n/a		n/a		43.2 n/a	n/a	n/a	n/a	n/a	n/a
24/04/2002			91.0	10.0	1000	11	Unchanged			7.9	2.89	9.4	1.1	97.7	32.5	33.3	22.0		152	4.56				39.1					
22/05/2002			91.0	10.0	1000	11	Unchanged			8.0	2.94	9.7	1.4	101.1	33.3	32.6	22.6		186	4.32				40.9					
+8 Months		8	91.0	10.0	1000	11	Unchanged		n/a	8.0	2.92	9.6	1.3	99.4	32.8	33.0	22.3 n/a		169	4.45 n/a		n/a		40.0 n/a	n/a	n/a	n/a	n/a	n/a
26/06/2002			91.0	10.0	1000	11	Unchanged			8.0	2.88	9.8	1.5	104.0	34.2	32.9	22.2		194	4.88									
24/07/2002			91.0	10.0	1000	11	Unchanged			8.8	3.11	10.5	2.2	103.4	33.7	32.5	22.2		187	4.88		3.5	108.8	45.3	51.2		3.5		
+10 Months		10	91.0	10.0	1000	11	Unchanged		n/a	8.4	3.00	10.2	1.9	103.7	34.0	32.7	22.2 n/a		191	4.78 n/a		3.5	108.8	45.3	51.2 n/a	n/a	3.5	n/a	n/a
21/08/2002			90.0	9.0	1000	11	Unchanged		0	8.7	3.01	10.0	1.7	103.2	33.4	32.3	21.1		197	4.01		3.2	96.3	44.0					
18/09/2002			94.0	13.0	1000	11	Unchanged		0	8.0	3.10	10.3	2.0	102.9	33.2	32.2	21.8		202	5.28		3.4	105.4	42.9	49.5		4.4	3.2	
+12 Months		12	92.0	11.0	1000	11	Unchanged		0	8.4	3.06	10.2	1.9	103.1	33.3	32.3	21.5 n/a		200	4.65 n/a		3.3	100.9	43.5	49.5 n/a	n/a	4.4	3.2 n/a	n/a
*12 Months Summary		12	92.0		1000	11	Unchanged		0	8.4	3.06	10.2	1.9	103.1	33.3	32.3	21.5 n/a		200	4.65 n/a		3.3	100.9	43.5	49.5 n/a	n/a	4.4	3.2 n/a	n/a
30/10/2002			94.0	13.0	1000	11	Unchanged		0	7.6	2.79	9.4	1.1	103.7	33.5	32.3	21.2		172	4.37		3.2	89.0	44.8					
27/11/2002			95.0	14.0	1000	11	Unchanged		0	8.4	2.90	10.0	1.7	104.5	33.7	32.0	20.9		168	5.12		2.9	83.0	45.6					
+14 Months		14	94.5	13.5	1000	11	Unchanged		0	8.0	2.85	9.7	1.4	104.1	33.7	32.2	21.1 n/a		170	4.75 n/a		3.0	86.0	45.2 n/a	46.2	n/a	4.1	n/a	n/a
08/01/2003			96.0	15.0	1000	10	Unchanged		0	8.0	3.28	11.1	2.8	103.8	33.9	32.6	21.3		208	5.80	1	3.6	118.0	44.5	46.2 n/a	n/a	4.1	5.2	n/a
+16 Months		16	96.0	15.0	1000	10	Unchanged		0	8.0	3.28	11.1	2.8	103.8	33.9	32.6	21.3 n/a		208	5.80 n/a		3.6	118.0	44.5	46.2 n/a	n/a	4.1	5.2 n/a	n/a
05/03/2003			96.0	15.0	1000	10	Unchanged		0	7.9	2.89	9.6	1.3	104.5	33.3	31.8	21.7		185	4.34				43.1	47.2		4.2	5.5	
+18 Months		18	95.0	14.0	1000	11	Unchanged		0	7.9	2.89	9.6	1.3	104.5	33.3	31.8	21.7 n/a		185	4.34 n/a		2.5	69.0	43.1	47.2 n/a	n/a	4.2	5.5 n/a	n/a
16/04/2003			95.0	14.0	1000	11	Unchanged		0	7.6	2.77	9.4	1.1	104.5	34.1	32.6	22.1		154	4.03									
22/05/2003			94.5	13.5	1000	11	Unchanged		0	7.9	3.21	10.3	2.0	103.7	32.1	30.9	21.0			3.96									
+20 Months		20	94.8	13.8	1000	11	Unchanged		0	7.8	2.99	9.9	1.6	104.1	33.1	31.8	21.6 n/a		154	4.00 n/a		2.5	69.0	47.8 n/a	n/a	n/a	n/a	n/a	n/a
11/06/2003			94.0	13.0	1000	11	Unchanged		0	7.8	3.12	10.6	2.3	104.4	33.8	32.4	20.9		159	4.14		3.3	103.0	45.3					
+22 Months		22	94.0	13.0	1000	11	Unchanged		0	7.8	3.12	10.6	2.3	104.4	33.8	32.4	20.9 n/a		159	4.14 n/a		3.3	103.0	45.3 n/a	46.2 n/a	n/a	4.1	n/a	n/a
06/08/2003			95.0	14.0	1000	10	Unchanged			7.6	3.11	10.4	2.1	105.3	33.4	31.7	21.2		169	4.15		3.3	103.0	46.0					
+24 Months		24	95.0	14.0	1000	11	Unchanged		n/a	7.6	3.11	10.4	2.1	106.3	33.4	31.7	21.2 n/a		169	4.15 n/a		3.3	103.0	46.0 n/a	47.2 n/a	n/a	4.2	n/a	n/a
*24 Months Summary		24	95.0		1000	11	Unchanged		n/a	7.6	3.11	10.4	2.1	106.3	33.4	31.7	21.2 n/a		169	4.15 n/a		3.3	103.0	46.0 n/a	47.2 n/a	n/a	4.2	n/a	n/a
01/10/2003			92.0	11.0	1000	10	Unchanged			7.9	2.92	10.2	1.9	106.9	35.0	32.7	21.0		205	4.20		3.2	93.0	47.8					
26/11/2003			91.0	10.0	1000	10	Unchanged			7.8	3.05	10.3	2.0	106.1	33.9	31.9	20.8		199	4.60				45.9					
+26 Months		26	91.5	10.5	1000	10	Unchanged		0	7.9	2.99	10.3	2.0	106.5	34.5	32.3	20.9 n/a		202	4.40 n/a		3.2	93.0	46.9 n/a	n/a	n/a	n/a	n/a	n/a
21/01/2004			92.0	11.0	1000	11	Unchanged			7.7	3.05	10.0	1.7	105.0	32.9	31.3	20.9		193	3.95		3.7	113.0	46.0					
+28 Months		28	92.0	11.0	1000	11	Unchanged		n/a	7.7	3.05	10.0	1.7	105.0	32.9	31.3	20.9 n/a		193	3.95 n/a		3.7	113.0	47.8 n/a	47.2 n/a	n/a	4.2	n/a	n/a
17/03/2004			94.5	13.5	750	8	Decreased			7.9	2.90	9.8	1.5	104.1	33.6	32.3	20.5		221	4.73				47.2					
+30 Months		30	92.0	11.0	750	8	Decreased		n/a	7.9	2.90	9.8	1.5	104.1	33.6	32.3	20.5 n/a		221	4.73 n/a				47.2 n/a	40.1		4.0	125.0	n/a
28/04/2004			94.5	13.5	750	8	Unchanged		0	8.6	3.13	10.1	1.8	101.3	32.3	31.9	21.2		201	6.54		4.0	125.0	40.1					
+32 Months		32	94.5	13.5	750	8	Unchanged		0	8.6	3.13	10.1	1.8	101.3	32.3	31.9	21.2 n/a		201	6.54 n/a		4.0	125.0	40.1 n/a	40.1 n/a	n/a	n/a	n/a	n/a
*36 Months Summary		32	94.5		750	8	Unchanged		0	8.6	3.13	10.1	1.8	101.3	32.3	31.9	21.2 n/a		201	6.54 n/a		4.0	125.0	40.1 n/a	40.1 n/a	n/a	n/a	n/a	n/a

NHS

London (North West) Haemoglobinopathy Registry

NHS No:	1234567890
Hospital ID No:	1234567

Patient: Firstname SURNAME

HU Status: Unchanged - 28/04/2004

Date	Birth Date	Months on HU	Na	K	Urea	Creatinine	AST	ALT	gGT	Bilirubin Total	Protein Total	Albumin	Alk. Phos.	LDH	ZPP	Serum Fe	TIBC	Ferritin	Serum B12	Red Cell Folate	PT	PTTK	IP	IP No Days	IP Hospital	IP Diagnosis
03/10/2001			141	4.2	4.5	109	66			77			101	891										5	65 CMH	Other=Lap Chole, Gallbladder Disease, ERCPS
17/10/2001			141	5.5	6.5	117	57	57		51		44	86					727					Yes	2 CMH		Other=SCD ERCP
31/10/2001			141	4.5	4.8	94	54			47		42	89	692				612					No			
07/11/2001																							No			
21/11/2001			139		4.1					35		44											No			
+2 Months		2	140	5.0	5.1	106	56			44	n/a	43	88	692	n/a	n/a	n/a		n/a	n/a	n/a	n/a	Yes	2		
02/01/2002			139	4.0	4.5	87	57			26		43	82	532									No			
+4 Months		4	139	4.0	4.5	87	57	n/a		26	n/a	43	82	532	n/a	n/a	n/a		n/a	n/a	n/a	n/a	No	n/a		
13/02/2002			140	4.0	5.7	96				18		45	78	388									No			
27/02/2002																							No			
13/03/2002			141	4.3	3.9	98	42			19		43	76	368									No			
27/03/2002																							No			
+6 Months		6	141	4.2	4.8	97	43	n/a		19	n/a	44	77	373	n/a	n/a	n/a		n/a	n/a	n/a	n/a	No	n/a		
24/04/2002			140	4.0	6.0	96	41			25		43	86	487									No			
22/05/2002			142	4.0	5.1	98	36			24		44	78										No			
+8 Months		8	141	4.0	5.6	97	39	n/a		25	n/a	44	82	487	n/a	n/a	n/a		n/a	n/a	n/a	n/a	No	n/a		
26/06/2002			141	4.3	5.9	105	50	76		28		46	78								16.0		No			
24/07/2002								88		25		43	73		31			938					No			
+10 Months		10	141	4.3	5.9	105	53	82		27	n/a	45	76		31	n/a	n/a	938	n/a	n/a	16.0	n/a	No	n/a		
21/08/2002			140	4.1	5.3	97	38			23		43	77										Yes	1 CMH		Other=SCD ERCP
18/09/2002			140	4.1	4.7	88	34			21		46	77	496									No			
+12 Months		12	140	4.1	5.0	93	36			22	n/a	45	77	496	n/a	n/a	n/a		n/a	n/a	n/a	n/a	Yes	1		
*12 Months Summary		12	140	4.1	5.0	93	36	n/a		22	n/a	45	77	496	n/a	n/a	n/a		n/a	n/a	n/a	n/a	2	3		Other=2
30/10/2002			141	4.6	6.2	94	47			20		46	67	641				727					No			
27/11/2002			142	4.1			51			22		41	72	446				612					No			
+14 Months		14	141	4.6	6.2	94	49	n/a		21	n/a	44	70	544	n/a	n/a	n/a	670	n/a	n/a	n/a	n/a	No	n/a		
08/01/2003			142	4.1	4.6	97	79			26		51	84	524				776					No			
+16 Months		16	142	4.1	4.6	97	79	n/a		26	n/a	51	84	524	n/a	n/a	n/a	776	n/a	n/a	n/a	n/a	No	n/a		
05/03/2003			142	4.2	4.5	96	62			23		42	80	564				799					No			
+18 Months		18	142	4.2	4.5	96	62	n/a		23	n/a	42	80	564	n/a	n/a	n/a	799	n/a	n/a	n/a	n/a	No	n/a		
16/04/2003			139	4.4	6.3	96	66			20		42	62	560									No			
22/05/2003							119	84		33		46	76										No			
+20 Months		20	139	4.4	6.3	96	93	84		27	n/a	44	69	560	n/a	n/a	n/a	1605	n/a	n/a	n/a	n/a	No	n/a		
11/06/2003			138	4.1	5.7	102	116			24		37	66	446									No			
+22 Months		22	138	4.1	5.7	102	116	n/a		24	n/a	37	66	446	n/a	n/a	n/a	1605	n/a	n/a	n/a	n/a	No	n/a		
06/08/2003			141	4.7	4.7	103	102			25		44	73	535				1170					No			
+24 Months		24	141	4.7	5.1	103	102	n/a		25	n/a	44	73	535	n/a	n/a	n/a	1170	n/a	n/a	n/a	n/a	No	n/a		
*24 Months Summary		24	141	4.7	5.1	103	102	n/a		25	n/a	44	73	535	n/a	n/a	n/a	1170	n/a	n/a	n/a	n/a	0	0		
01/10/2003			140	4.4	5.2	92	85			20		44	66	529									No			
26/11/2003			141	4.7	5.4	94	71			23		44	60	460					268	589	14.1		No			
+26 Months		26	141	4.6	5.3	93	93	n/a		22	n/a	44	63	495	n/a	n/a	n/a	1605	268	589	14.1	n/a	No	n/a		
21/01/2004			143	4.3	4.9	96	74			25		44	64	526				1006					No			
+28 Months		28	143	4.3	4.9	95	74	n/a		25	n/a	44	64	526	n/a	n/a	n/a	1006	n/a	n/a	n/a	n/a	No	n/a		
17/03/2004			142	4.6	7.0	97	74			20		45	64	544				926					No			
+30 Months		30	142	4.6	7.0	97	74	n/a		20	n/a	45	64	544	n/a	n/a	n/a	926	n/a	n/a	n/a	n/a	No	n/a		
28/04/2004			141	4.3	4.5	97	70			25		44	69	524				911		911	15.6		No			
+32 Months		32	141	4.3	4.5	97	70	n/a		25	n/a	44	69	524	n/a	n/a	n/a	911	n/a	911	15.6	n/a	No	n/a		
*36 Months Summary		32	141	4.3	4.5	97	70	n/a		25	n/a	44	69	524	n/a	n/a	n/a	911	n/a	911	15.6	n/a	0	0		

NHS No: 1234567890 **Hospital ID No: 1234567**

Patient: Firstname SURNAME **HU Status: Unchanged - 28/04/2004**

NHS

Date	Birth Date	Months on HU	Pain in Community	Pain in Community Description	Calculated Toxic Episodes	Comments/Problems	Blood Tx	Units In	Vene-section	Units Out	Date of LMP	Contraception	Follow-up Appointment (Weeks)
03/10/2001			Yes	Throbbing pains all		Repeat biliary problems, c/o Lethargy	Sporadic						2
17/10/2001			Yes	Throbbing pains redu									2
31/10/2001			No										1
07/11/2001			Yes	Chest pain no abdo p		Back Pain, Shoulder Pain							2
21/11/2001			No			Occ. Rotten Days							4
+2 Months		2	No		0	Nausea and Itching, O		0		n/a			6
+4 Months		4	No		0			0		n/a			6
13/02/2002			No										6
27/02/2002			No			Head, Chest, Shoulder							2
13/03/2002			No				Top-Up	3					2
27/03/2002			No										4
+6 Months		6	Yes	RUQ, periodic	0			3		n/a			4
24/04/2002			Yes	Soreness around oper		Tingling sensation a							5
+8 Months		8	Yes	Pain right side abdo	0	Light headed		0		n/a			4
24/07/2002			Yes	Pain right side abdo									4
+10 Months		10	Yes	Pain in Rt side	0			0		n/a			4
18/09/2002			Yes	SLIGHT PAIN RT SIDE OF ABDO		ERCP NORMAL							6
+12 Months Summary		12			0			0		n/a			
+12 Months		12	No			LEG ULCER (R), FROM MOSQUITO BITE							4
27/11/2002			Yes	PAIN IN RT SIDE PAIN IN H KNEE		LEG ULCER (R)							
+14 Months		14	Yes	ULCER 6/12 - R FOOT	0	BP = 145/78		0		n/a			8
+16 Months		16	No		0	ULCER SMALL R FOOT BP = 142/79		0		n/a			6
+18 Months		18	No		0	CHEST TIGHTNESS O/E		0		n/a			8
22/05/2003			No			RESULTS FROM GASTRO CLINIC							
+20 Months		20	No		0	HAIR LOSS, CHEST PAIN, TIREDNESS		0		n/a			8
+22 Months		22	No		0	FASTING GLUCOSE 12.7		0		n/a			8
+24 Months		24	No		0			0		n/a			
+24 Months Summary		24			0			3		n/a			
01/10/2003			No			TIREDNESS, CHEST XRAY ABNORMAL							8
28/11/2003			No			CHEST TIGHTNESS BP = 169/83							8
+26 Months		26	No		0	CHEST PAIN, ERCP NEG, BP UP		0		n/a			8
+28 Months		28	Yes	PAIN FROM LEG ULCERS	0	3R + 1 LEG ULCER, ? HU TOXIC		0		n/a			6
+30 Months		30	Yes	KNEES		HAS VARICOSE VEINS BOTH LEGS		0		n/a			8
+32 Months		32			0			0		n/a			
+36 Months Summary		36			0			0		n/a			

MCV, Hb F and Hb & HU Dose - (03/10/2001 - 28/04/2004)

NHS No: 1234567890

Patient: Firstname SURNAME

Hospital ID No: 1234567

HU Status: Unchanged - 28/04/2004

Retics and Neutrophils & HU Dose - (03/10/2001 - 28/04/2004)

NHS No: 1234567890   Hospital ID No: 1234567

Patient: Firstname SURNAME   HU Status: Unchanged - 28/04/2004

Creatinine, Bilirubin, AST and ALT & HU Dose - (03/10/2001 - 28/04/2004)

NHS No: 1234567890

Patient: Firstname SURNAME

Hospital ID No: 1234567

HU Status: Unchanged - 28/04/2004

Appendix V: NWL Registry Annual Report

Haemoglobinopathy Registry: Annual Report for CMH - 2006/2007

HAEMOGLOBINOPATHY REGISTRY

ANNUAL REPORT FOR CENTRAL MIDDLESEX HOSPITAL - 2006/2007

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1. BACKGROUND

The Haemogloginopathy Registry is a multicentre registry based in the Haematology Department of Central Middlesex Hospital (CMH), London. It was initiated in 1998, as collaborative effort between 10 European countries and was later developed, in 2001, into a comprehensive database for all patients with sickle cell disease (SCD) and thalassaemia attending local hospitals in the North West London (NWL) Health Sector. It collects longitudinal demographic, clinical and psychosocial information on patients who attend hospitals participating in the Registry.

Funding from the local primary care trusts (PCTs) enabled local hospitals to participate but this funding ceased in March 2004. Brent PCT continues to partially fund the database which facilitates the continuation of registry activities for Brent patients attending CMH. This report will describe the local aims and objectives of the registry, its processes and progress, benefits to patients and health agencies and local patient demography.

2. METHODS

2.1 Aims and objectives
The registry **aims** to directly support clinical care and improve patient treatment and outcomes and to enable equitable and effective provision of health services within the local Health Community.

Objectives
- Accurate information for clinical management of patients, clinical governance & audit
- Accurate information for planning acute and community services
- Evaluation of interventions (e.g. hydroxyurea treatment)
- Study the natural history of the haemoglobinopathies
- Collaboration and information sharing

2.2 Operational procedures
The registry is registered under UK data protection legislation and has Research Ethics Committee approval. Patients give their written consent to have their clinical data entered into the database and for its potential use in research. There are standardized data collection materials and automated data validation, processing and clinical reporting systems. The registry requires an initial registration questionnaire to be completed for all patients and an annual follow-up. The information collected is routine, as normally recorded in hospital medical records. It includes demographics, past medical history, psychosocial, clinical, treatment and laboratory data. There are effective quality control procedures and protocols. A registry website has been developed for the benefit of patients/carers, health professionals and members. It provides information and resources about the registry, local acute and community health services, relevant reports and patient care protocols.

2.3 Patient participation

There were 676 sickle and thalassaemia patients registered at CMH as an inpatient or outpatient by January 2007. Seventy seven percent (522) have given consent for their clinical information to be entered into the registry. Reasons for non consent include: not approached, ineligible, inappropriate or refused. About 10% of eligible patients (those with a major sickle syndrome) remain to be consented. It will be difficult to gain consent from this group as they are not regular hospital attendees or they have not attended the outpatient clinic for a long time. For patients that have been approached the consent rate is in excess of 95%. Since 1 April 2006 no new attendee refused consent but three patients already known to the hospital continue to refuse to be part of the registry. In a small number of cases it is inappropriate to ask the patients to consent to joining the registry because they are unable to make an informed decision during the consultation. This occurs if the patient attends without an interpreter and has insufficient English language skills, the patient is a minor and attends without their legal guardian or the patient is incapable of fully comprehending the request.

2.4 Data management

There is clinical data entered on the registry for 377 patients, which represents 72% of consented patients. The average length of follow-up for these patients is 9.5yrs (SD 9yrs, range 0 months -42yrs).

3. RESULTS

3.1 Benefits

The main benefits of the registry to patients, service providers and purchasers are as follows:

a) Anonymous aggregated demographic and clinical reports are provided, as required, for local audits, service management, service planning and needs assessment (see figures 1a,1b,2a,2b,3a,3b). For example Brent PCT recently requested a report about numbers of SCD children in Brent split into specific age and ethnic groups. Departmental audits using registry data include: patients with antibodies acquired through blood transfusion, pregnancy outcomes and health outcomes following treatment with CPAP[1] in the management of Acute Chest Syndrome. Registry information is frequently utilized to identify cohorts of patients for potential participation in research and audit projects.

b) Automated reporting systems produce comprehensive individualised patient reports for clinical management (see Appendices: figure 4 and 5). Figure 4 shows a graphic report summarizing key haematological and clinical information essential for monitoring a patient's response to hydroxyurea (HU) treatment. Hydroxyurea is used for ameliorating the clinical severity of SCD. It is a chemotherapeutic agent that can prove toxic to patients in certain circumstances. Patients need regular and

close monitoring whilst on HU to assess short and long-term response to treatment and clinical benefit, avoid toxicity and adverse affects. Relevant clinical data is collected at each clinic visit on all patients taking HU which enables the registry to produce individual patient and group reports. Figure 5 is an example of a patient report, providing a succinct summary of the patient's demographics, medical history, current treatment and care.

c) Audit current clinical practice against 'recommended and best practice'. Registry outputs can be utilized internally and by local agents, such as the North West London Haemoglobinopathy Managed Clinical Network, to evaluate current practice against standards and guidelines set by the Sickle Cell and Thalassaemia Screening Program[2].

3.2. CMH Haemoglobinopathy Services Report for 2006-2007

3.2.1 Patient numbers and characteristics: PCT of residence

There were 676 SCD and thalassaemia patients registered at CMH as an inpatient or outpatient by January 2007. This represents an increase of over 8% from the previous year when 624 patients were registered (at 31/03/2006). In the main the new patients came from the local PCTs of Brent, Harrow and Hillington (see figures 1a,1b). Ten, however, were from outside the NWL Sector which may be attributed to the fact that CMH attracts patients from all over the UK due to its reputable acute and community haemoglobinopathy services. The increase has not changed the proportions of patients attending from each PCT. In accord with previous years about half the patients attending live in Brent, 1/5 in Harrow, 1/5 in the rest of the NWL sector and the remaining patients come from other parts of London, the UK or overseas.

Figure 1a

Central Middlesex Hospital Haemaglobinopathy Patients by PCT of Residence (624 Patients) 2005-06

Overseas, 5, 1%
Hounslow, 9, 1%
UK, 40, 6%
Hammersmith&Fulham, 15, 2%
Other London, 62, 10%
Westminster, 8, 1%
Kensington&Chelsea, 1, 0%
Ealing, 42, 7%
Hillingdon, 15, 2%
Harrow, 129, 21%
Brent, 298, 49%
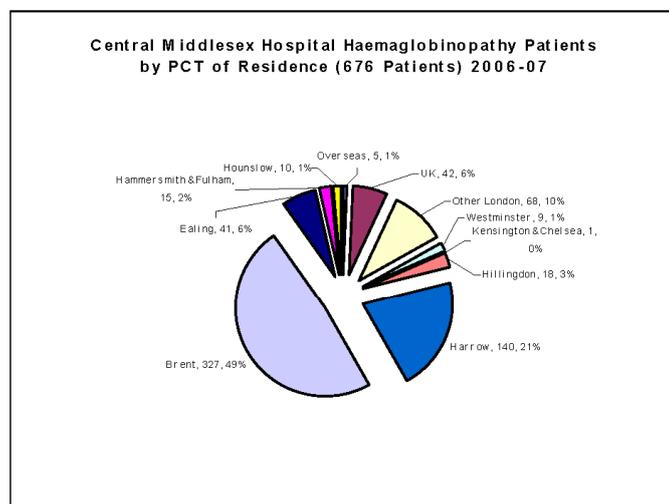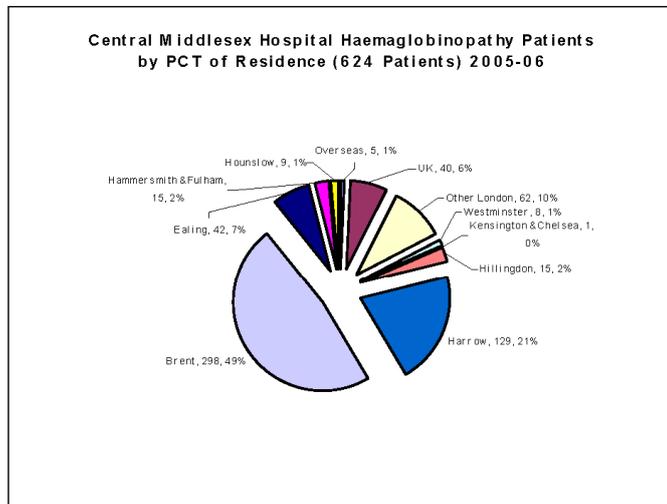
Figure 1b

3.2.2 Patient characteristics: age profile

The age profile of patients attending CMH is shown in figures 2a and 2b. This remains similar to the previous year. Thirty percent of patients are children, another 8% are older teenagers/ young adults and the remaining 62% are adults of 20 years and older. The only change since last year is a 2% increase in children and 2% decrease in adults between the ages of 31-50 years.

Central Middlesex Hospital Haemaglobinopathy Patients by Age Group (676 Patients) 2006-07

>50 Years
45
7%

0-15 Years
203
30%

31-50 Years
228
33%

16-19 Years
53
8%

20-30 Years
147
22%

Figure 2a

Central Middlesex Hospital Haemaglobinopathy Patients by Age Group (624 Patients) 2005-06

>50 Years
43
7%

0-15 Years
173
28%

31-50 Years
218
35%

16-19 Years
52
8%

20-30 Years
138
22%
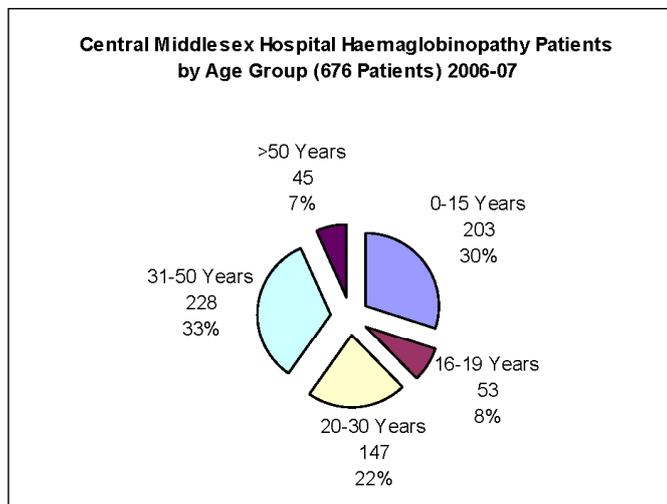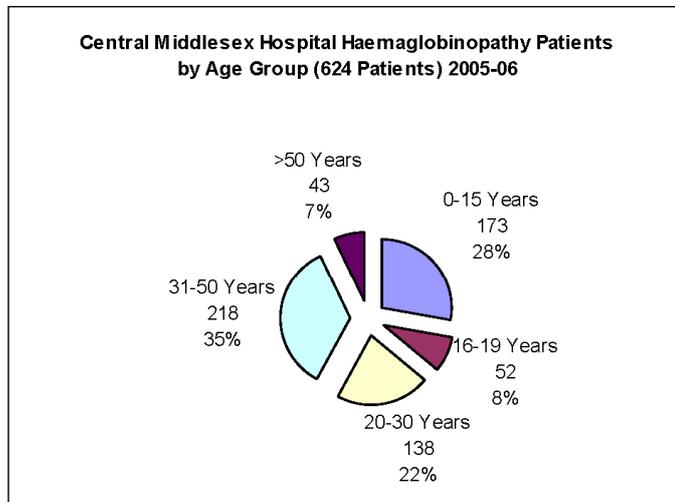
Figure 2b

3.2.3 Patients characteristics: disease profile

The disease profile of patients, as shown in figure 3a and 3b, remains largely unchanged from previous years. The vast majority of patients have sickle cell disease (> 86%). Only 5% of current patients suffer from thalassaemia syndromes, a decrease of 2% from last year. It is not possible to determine from the data why this decrease occurred. A possible reason is a change in local population ethnicity, with a decrease in ethic groups who are at risk of thalassaemia. Another possibility is a change in patients preferences and/or local referral patterns for health services for thalassaemia patients.

Central Middlesex Hospital Haemaglobinopathy Patients by Haemoglobinopathy Type (676 Patients) 2006-07

Missing Diagnosis 4%

Other 5%

Thal Syndromes 5%

SBThal 9%

SS 56%

SC 21%

Figure 3a

Central Middlesex Hospital Haemaglobinopathy Patients by Haemoglobinopathy (624 Patients)Type 2005-06

Other 4%
Missing Diagnosis 4%
Thal Syndromes 7%
SBThal 9%
SS 57%
SC 21%
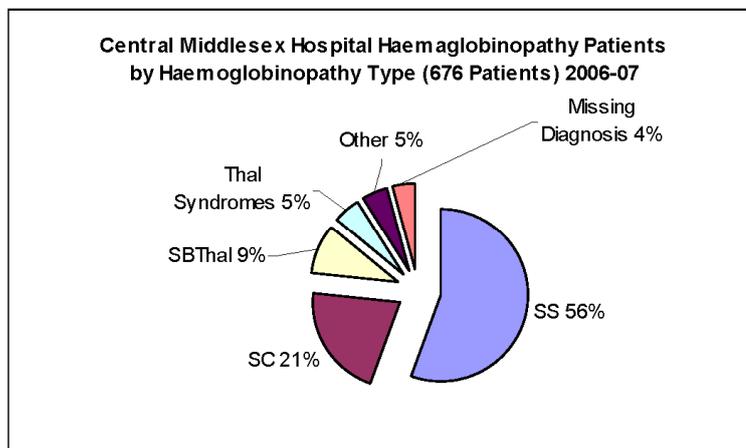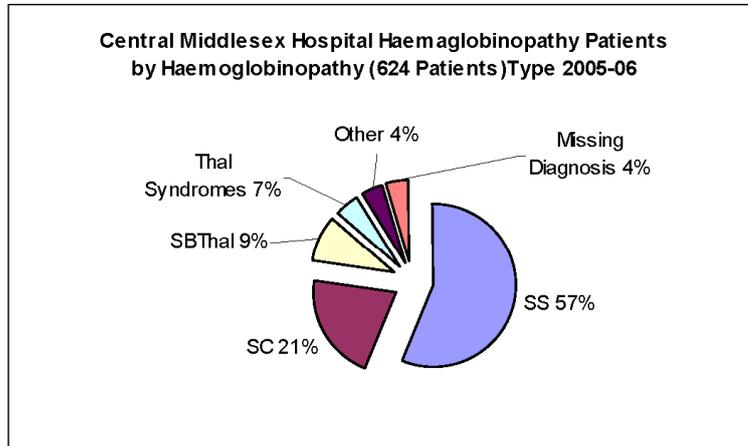
Figure 3b

Date: January 2007

Footnote:
1. CPAP = Continuous positive airway pressure
2. Dick M (2006) *Sickle cell disease in childhood: standards and guidelines for clinical care*. NHS Sickle Cell and Thalassaemia Screening Programme in partnership with the Sickle Cell Society. www.screening.nhs.uk/sickleandthal

APPENDIX 1
Figure 4

APPENDIX 2

Figure 5

European Haemoglobinopathy Registry Report

NHS

EHR — European Haemoglobinopathy Registry

NHS No:	1234567890
Hospital ID No:	123456
Patient:	Firstname SURNAME
Consultant:	CONSULTANT
Hospital:	NHS
Sex:	Male
Date of Birth:	01/01/1980
Hospital Location:	UK
Age:	22
Initial EHR Review:	25/04/2002
Last Annual Follow-up:	25/04/2002
Annual Follow-up:	April 2003

Demographics

NHS Number	1234567890
Hospital ID Number	123456
Patient Name	Firstname SURNAME
Postcode	ABC 123
Date of Birth	01/01/1980
Age	22
Sex	Male
Consultant	CONSULTANT
Hospital	NHS
Hospital Location	UK
Date of Initial EHR Review	25/04/2002
Date of Annual Follow-up Due	April 2003
First SCD Presentation at Your Hospital	1986
Ethnic Origin	Caribbean
Hb Type	SS
Alpha Thal Trait	Not known
G6PD Deficiency	No
RBC Phenotyped	***Missing Data***
RBC Allo Antibodies	***Missing Data***
Diagnosis Made By	Symptomatic Presentation
Age at Diagnosis	18 Months

Medical History:

Inpatient Pain Crisis	Yes
	2 IP Pain Events in the Last Year

Report produced by: European Haemoglobinopathy Registry - Haematology Department - Central Middlesex Hospital - The North West London Hospitals NHS Trust, from the information provided by the data collector at NHS Hospital.

Notice and Disclaimer:
The information provided in this report is collected from the patient's medical records. Although care has been taken in gathering this information and preparing this report, the European Haemoglobinopathy Registry cannot guarantee the accuracy and completeness thereof. The European Haemoglobinopathy Registry accepts no liability whatsoever for the information provided in this report. This report is for use by a qualified health care provider. If in any doubt, please consult the patient's Hospital Consultant.

MREC Registration No: MREC/99/2/4
Last updated 04-12-2003

Data Protection Act 1998 Registration No: Z5730583
Printed 14-04-2005
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NHS

EHR — European Haemoglobinopathy Registry

NHS No:	1234567890	**Hospital ID No:** 123456
Patient:	Firstname SURNAME	

|		
Avascular Necrosis	No	
Hearing Impairment	Yes	Temporary
Acute Chest Syndrome	1st Event	Nov 1988
Acute Chest Syndrome	2nd Event	Nov 2001
Infarctive Stroke	1 Event	1st Event 1991
Blood Tx (inc. Exchange Tx)	Yes - ***Calculated Value***	
Exchange Tx	Yes - ***Calculated Value***	
Previous Tx Programme Started	Yes	1991
Tx Programme Stopped	01/04/2001	
Previous Chelation	***Missing Data***	

CNS Event 1

Hospital ID Number	***Hospital ID Numbers do NOT Match! - ***ERROR***	
Event Number	1	
Date of Presentation	29/08/1991	
Type of Event	Infarctive Stroke	
Family History:		
History of Fits	No	
History of Febrile Consulsions	No	
Family History of Epilepsy	No	
Relatives with SCD Neurological Complications		

Description of Event:

Side of Body Affecte	Right	
Part(s) of Body Affected	HAND ARM LEG	
Investigations		
CAT Scan	Yes - Abnormal	September 1991: HAMMERSMITH
MRI	Yes - Abnormal	September 1991: HAMMERSMITH
Sleep Study (off Tx)	Yes - Normal	July 1986: BROMPTON
Long Term Management:	Tx Programme	
Outcome/Long Term Effects:		
Physical Disabilities	Yes	
Learning Difficulties	Yes	
Other	Yes - (BEHAVIOURAL PROBLEMS)	

Blood Transfusion Programme 1

Hospital ID Number	***Hospital ID Numbers do NOT Match! - ***ERROR***	
Type of Programme Commenced	Manual Exchange Tx	01/09/1991
Indications for Starting Tx Programme	Stroke	
Aims:	Planned Period	36 Months
Tx Programme Stopped	Yes	01/04/2001

Other Illness/Conditions/Operations

REPAIR OF CONGE VITAL HEART DEFECT PATIAL RIGHT PULMONARY		1990

Report produced by: European Haemoglobinopathy Registry - Haematology Department - Central Middlesex Hospital - The North West London Hospitals NHS Trust, from the information provided by the data collector at NHS Hospital.

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MREC Registration No: MREC/99/2/4
Last updated 04-12-2003

Data Protection Act 1998 Registration No: Z5730583
Printed 14-04-2005
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Appendix VI: NWL Registry publication

Longitudinal analysis of pulmonary function in adults with sickle cell disease

Longitudinal analysis of pulmonary function in adults with sickle cell disease

Joshua J. Field,[1]* Jeffrey Glassberg,[2] Annette Gilmore,[3] Joanna Howard,[2] Sameer Patankar,[3] Yan Yan,[4] Sally C. Davies,[3] Michael R. DeBaun,[5] and Robert C. Strunk[2]

Among adults with sickle cell disease (SCD), pulmonary complications are a leading cause of death. Yet, the natural history of lung function in adults with SCD is not well established. We conducted a retrospective cohort study of adults with SCD who had repeated pulmonary function tests performed over 20 years of age. Ninety-two adults were included in this cohort. Rate of decline in FEV_1 for men and women with SCD was 49 cc/year (compared with 20–26 cc/year in the general population). Further studies are needed to identify factors which impact the rate of lung function decline in adults with SCD. Am. J. Hematol. 83:574–576, 2008. © 2008 Wiley-Liss, Inc.

Introduction

Pulmonary disease is a common cause of morbidity and mortality among individuals with sickle cell disease (SCD) [1]. Acute pulmonary complications, such as acute chest syndrome (ACS), predominate in children, while chronic lung disease is more common in adults with SCD. ACS occurs in ~50% of individuals with SCD over the course of their lifetime [2]. Repetitive episodes of ACS may lead to sickle chronic lung disease, which is characterized by a restrictive pattern on pulmonary function testing [3]. Sickle chronic lung disease is the cause of death for 20% of adults with SCD [4].

Despite the significant contribution of pulmonary disease to SCD-related morbidity and mortality, pulmonary function test (PFT) abnormalities are not well described in adults with SCD. Klings et al. reports PFT results in a large cohort of adults with SCD ($n = 310$) who participated in the Cooperative Study of Sickle Cell Disease [5]. Abnormal PFTs are noted in 90% of individuals assessed. Restrictive physiology is the most common abnormality, present in 74% of adults. Other investigators also report restrictive lung disease in adults with SCD [3,6,7]; however, no study to date describes the longitudinal course of lung function among adults with SCD.

The primary objective of our study was to describe the changes in pulmonary function over time in adults with SCD. Further, we sought to describe the prevalence of abnormal patterns of pulmonary function in this cohort and the relationship of these abnormal patterns to SCD-related morbidity.

Results

Ninety-two adults with SCD who completed at least one PFT after 20 years of age were included in our cohort (Table I). The cohort consisted of 48% males and the mean age at last PFT was 36 years (range, 20–68 years). Of the 92 adults in the cohort, 49 individuals underwent repeated PFTs. Those with repeated measurements completed a mean of 2.6 PFTs. Participants were followed for a mean of 13 years. This cohort accrued 1330 patient-years of follow up. Twenty-three percent of the cohort smoked cigarettes at the time of pulmonary function testing. No participant was known to have a diagnosis of HIV.

Lung function significantly declined over time in adults with SCD (Fig. 1). After age 20 years, the rate of decline in FEV_1 among men and women with SCD was 49 cc/year. There was no difference in the decline of FEV_1 between

individuals with HbSS compared to a group comprised of the phenotypes HbSC, HbSβ-thalassemia[+], HbSβ-thalassemia[0], HbS-hereditary persistence of fetal hemoglobin, and HbSD ($P = 0.29$). Smoking cigarettes also did not significantly affect the decline in FEV_1 ($P = 0.07$). Similar to previous findings in adults with SCD [5], restrictive was more common than obstructive physiology (Table II). There was no association between increased rate of pain and subsequent restrictive (odds ratio 1.0, 95% CI 0.6–1.6, $P = 0.97$), or obstructive physiology (OR 0.5, 95% CI 0.2–1.1, $P = 0.09$), or abnormal FEV_1 (OR 1.4, 95% CI 0.9–2.3, $P = 0.14$); there was also no association between increased rate of ACS and subsequent restrictive (OR 1.9, 95% CI 0.6–6.1, $P = 0.28$), or obstructive physiology (OR 1.1, 95% CI 0.8–1.5, $P = 0.67$), or abnormal FEV_1 (OR 1.0, 95% CI 0.7–1.4, $P = 0.93$).

Discussion

Our study demonstrates that among adults with SCD, the rate of decline in lung function is greater than would be expected from historical controls without SCD [8]. Also, we have shown that the prevalence of restrictive lung disease in adults may be less than previously thought.

Cross-sectional studies of pulmonary function in adults with SCD demonstrate a reduced FEV_1 [3,5–7]. However, longitudinal assessment was not done to determine the rate of decline. In a nonsmoking individual without SCD, pulmonary function increases in childhood until about age 20 years, plateaus until age 35 years and then begins to decline at a rate of 20–26 cc/year [8–10]. An abnormal

TABLE I. Demographic and Morbidity Data for Total Cohort and Subgroup with Repeat Pulmonary Function Tests (PFT)

Cohort	Total	≥2 PFTs
No. Patients	92	49
Gender, %		
Male	48	43
Age last PFT, mean, y ± SD	36.2 ± 10.6	37.1 ± 9.2
Follow-up, mean, y ± SD	13.3 ± 10.2	13.5 ± 9.1
Phenotype, %		
SS	72	80
SC	16	12
Sβ-thalassemia^0	2	2
Sβ-thalassemia$^+$	7	4
SHPFH	2	2
SD	1	0
Smoked cigarettes, %	23	20
Pain admissions, no. #/year ± SD	0.9 ± 0.9	1.0 ± 0.9
ACS admissions, no. #/year ± SD	0.4 ± 1.3	0.2 ± 0.3
History of asthma, %	13	22

SHPFH, S-hereditary persistence of fetal hemoglobin; ACS, acute chest syndrome.

Figure 1. Longitudinal forced expiratory volume in 1 second adjusted for height in adults with sickle cell disease.

TABLE II. Pulmonary Function Tests in Adults with Sickle Cell Disease

PFT results, mean ± SD	
FEV$_1$ ($n = 92$)	78.9 ± 15.4
FVC ($n = 92$)	71.1 ± 15.6
FEV$_1$/FVC (%) ($n = 92$)	84.6 ± 8.0
RV ($n = 85$)	97.3 ± 61.5
TLC ($n = 84$)	86.7 ± 20.6
Below normal, %	
FEV$_1$	41.3
FVC	70.7
FEV$_1$/FVC (obstruction)	18.5
TLC (restriction)	35.7

FEV$_1$, Forced expiratory volume in 1 sec, FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.
Last pulmonary function measurement was analyzed.

adults with SCD (74%) [5]. Another limitation of our study was a small sample size for the purposes of studying factors that influence longitudinal changes in lung function, such as SCD phenotype. Although phenotype did not affect the rate of FEV$_1$ decline in our study, our small sample is prone to a type II error and thus our results must be interpreted with caution. Future studies are needed to better characterize the changes in lung function over time, and to identify factors that influence lung function decline.

In conclusion, the rate of decline in FEV$_1$ among adults with SCD is increased compared to the general population. Large, prospective studies of longitudinal pulmonary function are needed in children and adults with SCD so that risks of lung functions decline and its association with morbidity and mortality may be determined.

Methods

This study was approved by both Washington University School of Medicine Human Research Protection Office (St. Louis, MO) and the Research Ethics Committee of Central Middlesex Hospital (London, UK). From November 1, 1999 through March 1, 2005 individuals with SCD were enrolled in the European Haemoglobinopathy Registry (EHR). Informed consent to participate in the EHR allowed investigators to use participant's medical data for research purposes. Consent was obtained in accordance with the requirements and guidelines of the Research Ethics Committee at Central Middlesex Hospital.

Inclusion/exclusion

All patients at Central Middlesex Hospital with SCD who provided informed consent and underwent at least one outpatient pulmonary function assessment for clinical purposes were included. Lung volumes were done in a clinical laboratory using standard techniques with helium dilution. Individuals were required to have at least one PFT performed at 20 years of age or older to be included in the cohort. Carbon monoxide diffusing capacity (DLCO) was not included in this analysis because simultaneous hemoglobin values were not obtained and therefore adjustments for hemoglobin could not be performed. For cross-sectional analysis of PFT data, the last measurement was analyzed. Persons were excluded if inadequate follow up data existed, defined as less than 1 year of follow up at Central Middlesex Hospital.

Predicted pulmonary function values

Predicted values for FEV$_1$, FVC, FEV$_1$/FVC were obtained using the equations of Hankinson, et al, according to American Thoracic Society (ATS) criteria [12]. Predicted values for total lung capacity (TLC) and residual volume (RV) were obtained using the equations of Stocks and Quanjer, adjusting for race, according to ATS criteria [13]. Lower limit of normal was defined as values lower than the 5th percentile for an individual based on age, gender, race, and height.

FEV$_1$ in adults could be due to abnormal lung growth, a blunted plateau phase, an increased rate of decline or any combination of these factors. In our study, we could not assess lung growth because we did not include children in our cohort, and the plateau phase was difficult to assess due to our small sample size. The rate of decline in FEV$_1$ after 20 years of age (49 cc/year for men and women with SCD) was significantly greater than the rate of decline described in nonsmoking, non-SCD adults, 20–26 cc/year [8,10]. In the general population, poor lung function is an independent predictor of mortality [11]. The contribution of abnormal lung function to mortality among individuals with SCD is not known.

As with any retrospective study, our study has limitations. PFTs were obtained for clinical purposes and, thus, selection bias may have influenced our results. If this bias were significant, we would expect our adults to be more severely affected compared to those described in other studies. However, the percentage of adults in our study with restrictive lung disease (36%) is far less than described in the largest cross-sectional study of pulmonary function in

Definitions

Restrictive lung disease. Restrictive lung disease was defined as a TLC below the 5th percentile for an individual based on age, gender, race, and height [13].

Obstructive lung disease. Obstructive lung disease was defined as an FEV_1/FVC ratio below the 5th percentile for an individual based on age, gender, race, and height [12].

Pain episodes. A painful episode was defined as pain in the arms and legs, back, abdomen, chest or head that lasted at least 2 hr, lead to an admission to the hospital, and for which no other explanation was found (e.g., osteomyelitis or appendicitis) [14].

ACS episodes. An ACS episode was defined as new infiltrate on chest radiograph or a defect on radionuclide imaging of the chest, in combination with fever or respiratory symptoms [15].

Statistical data analysis

We used a multiple logistic regression model to study the relationship of restrictive and obstructive lung disease and abnormal FEV_1 with the number of prior pain and ACS episodes, adjusting for age. Longitudinal analysis of FEV_1 was performed using the generalized estimating equations method to model the association of FEV_1 with age and height, taking into account of correlations among repeated measurements within each study subject. To accommodate nonlinear relationships of age with the pulmonary functions, the restricted cubic spline functions were used. Empirical robust variances of parameter estimates were used for statistical inference. The Wald-type statistic was used for statistical inference of individual parameter, and the score statistic was used for the statistical inference of one variable in the presence of other variables. In our study sample, 87% of individuals with repeated FEV_1 measurements had between 2 and 4 measurements. We restricted the longitudinal analysis of FEV_1 to individuals with 2–4 repeated measurements to avoid forcing the FEV_1 trend of most participants (those with 2–4 measurements) to follow the trend of a few individuals (those with 5 or more measurements). Data were analyzed using SAS software v 9.1.

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Glossary

Adult haemoglobin (HbA) comprises over 95% of haemoglobin in an adult with normal haemoglobin. It has a $\alpha_2\beta_2$ (alpha$_2$beta$_2$) chain structure therefore each haemoglobin molecule has two α and two β polypeptide chains.

Erythrocyte
The mature non-nucleated red blood cell rich in oxygen carrying pigment haemoglobin.

Erythropoiesis
Maturation of the red blood cells, usually in the bone marrow.

Fetal haemoglobin (HbF)
In utero the fetus produces haemoglobin F which is replaced by normal HbA as it develops and during the first year of life. The chain structure of HbF is $\alpha_2\gamma_2$ (alpha$_2$gamma$_2$). In sickle cell disease a small amount of total haemoglobin persists as HbF after birth. The amount that persists varies between patients.

F Cell
A mature red blood cell with a high concentration of HbF.

F Reticulocyte (retic)
A young red blood cell containing a high concentration of HbF.

Globin
The protein parts of the haemoglobin molecule.

Haemoglobin molecule
The oxygen carrying part of red blood cells, composed of a closely integrated structure of four heme-globin units, called monomers. From infancy onward the majority of haemoglobin produced is adult haemoglobin (HbA). Haemoglobin is called oxyhaemoglobin when carrying oxygen and called deoxygenated haemoglobin when reduced of oxygen.

Haemoglobinopathy
This is a general term covering all inherited genetic disorders resulting from abnormal or underproduced haemoglobin proteins in the blood. An alteration occurs in the globin gene which results in the production of abnormal haemoglobin, underproduction or absence of globin. The abnormal haemoglobin results in sickle cell disease and the underproduction/absence of globin results in a thalassaemia syndrome. In a few cases both mechanisms occur (reduced synthesis of an abnormal haemoglobin e.g. HbE).

Rarely **acquired haemoglobinapathies** arise as a secondary manifestation of another disease, most commonly from haematologic premalignant conditions such as myelodysplastic and myeloproliferative syndromes. The condition is not restricted to any specific population group or geography. Other conditions classified as acquired haemoglobinopathies result from drug toxicity, for example carbon monoxide poisoning and methemoglobinaemia.

Infarction
Death of tissue caused by obstruction of the circulation.

Neutrophil (also call 'pus cell')
One of the cells that make up the polymorphonuclear leucocytes, the main phagocytic white cells in blood. They are collectively called granular cells.

Leucocyte
A white blood cell which includes lymphocytes, polymorphonuclear cells and monocytes.

Painful crisis (painful vaso-occlusive crisis)
The infarctive crisis that occurs after obstruction of the circulation by sickle cells in sickle cell disease.

Polymer
A substance formed by the linkage of a large number of smaller molecules known as monomers. When sickle haemoglobin is deoxygenated it can stick together to form crystalline groupings of haemoglobin or polymers. These polymers distort the red blood cells into sickle shapes.

Priapism
This is a prolonged painful erection of the penis that is not associated with sexual desire but caused by sickling in the corpora cavernosa with resultant blockage of the outflow vessels.

Reticulocyte (retic)
A young non-nucleated red blood cell. A raised retic count shows active erthropoiesis. The normal range is for retics to make up 0.2 or 2% of total red blood cells.

Serious Adverse Event
A clinical event which results in death, or is considered to be life-threatening for the patient.

Sickle cell anaemia
An inherited condition due to a single defective haemoglobin molecule, which results in the production of abnormal haemoglobin S (HbS) instead of normal haemoglobin A (HbA). It is characterised by sickle shaped red blood cells which are stiff and can block blood vessels.

Sickle cell disease (SCD)
This comprises the group of genetic conditions arising from the 'sickle' mutation. Inheriting the sickle gene from both parents' results in homozygous SCD (HbSS). An individual who inherits one sickle gene in combination with a sickle variant or a beta thalassaemia gene will have a heterozygous SCD. Clinically significant variant combinations include HbSC, HbSD^{Punjab}, HbSO^{Arab} and HbS/βthal syndromes.

Spermatogenesis
The process by which mature spermatozoa are produced in the testis.

Glossary

Thalassaemia
A group of inherited haemoglobinopathy disorders characterised by the underproduction of haemoglobin proteins resulting in anaemia of varying severity, depending on the form inherited. In beta thalassaemia major HbA is not produced at all and patients with this disorder suffer severe anaemia, requiring lifelong regular blood transfusions.

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